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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02076254.8

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JANSSEN PHARMACEUTICA N.V.
Turnhoutsebaan 30
2340 Beerse
BELGIQUE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Radiolabelled quinoline and quinolinone derivatives and their use as metabotropic
glutamate receptor ligands

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RADIOLABELLED QUINOLINE AND QUINOLINONE DERIVATIVES AND
THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR LIGANDS.

- 5 The present invention is concerned with radiolabelled quinoline and quinolinone derivatives showing metabotropic glutamate receptor antagonistic activity, in particular mGlu1 receptor activity, and their preparation ; it further relates to compositions comprising them, as well as their use in a diagnostic method, in particular for marking and identifying metabotropic glutamate receptor sites and for imaging an organ.

10

Introduction

- The neurotransmitter glutamate is considered to be the major excitatory neurotransmitter in the mammalian central nervous system. The binding of this neurotransmitter to metabotropic glutamate receptors (mGluRs), which are a subfamily
15 of the G-protein-coupled receptors and which comprise 8 distinct subtypes of mGluRs, namely mGluR1 through mGluR8, activates a variety of intracellular second messenger systems. The mGluRs can be divided into 3 groups based on amino acid sequence homology, the second messenger system utilized by the receptors and the pharmacological characteristics. Group I mGluRs, which comprises mGluR subtype 1
20 and 5, couple to phospholipase C and their activation leads to intracellular calcium-ion mobilization. Group II mGluRs (mGluR2 and 3) and group III mGluRs (mGluR4, 6, 7 and 8) couple to adenylyl cyclase and their activation causes a reduction in second messenger cAMP and as such a dampening of the neuronal activity. Treatment with Group I mGluR antagonists has been shown to translate in the parasynapsis into a
25 reduced release of neurotransmitter glutamate and to decrease the glutamate-mediated neuronal excitation via postsynaptic mechanisms. Since a variety of pathophysiologic processes and disease states affecting the central nervous system are thought to be due to excessive glutamate induced excitation of the central nervous system neurons, Group I mGluR antagonists, in particular mGluR1 antagonists could be therapeutically
30 beneficial in the treatment of central nervous system diseases, in particular in psychiatric and neurological diseases.

- However, up to now, no specific mGluR1-ligands were available, a lack severely hampering the study of the mGlu1 receptors, in particular the radioautographic
35 investigations of the unequivocal distribution and abundance of these receptors in brain sections.. For group I, only [³H]glutamate was available so far, being used on rat (Thomsen et al., Brain Res. 619, 22-28, 1993) or human (Kingston et al., 1998) mGlu1a

receptors. For the mGlu1a receptor and the mGlu5 receptor [³H]quisqualate is available, however, said receptor is not specific for the mGlu1 receptor (it also binds to the AMPA receptor) and it is competitive, i.e. it displaces glutamate (Mute1 at al., J. Neurochem., 75, 2590-2601, 2000).

5

It has been the goal of this invention to provide suitable specific, in particular non-competitive mGlu1-receptor ligands.

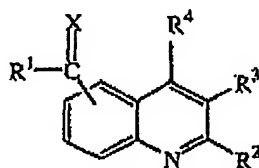
The inventors have now found a particular group of compounds that - in a radiolabelled
10 form - provides for suitable specific, in particular non-competitive mGlu1 receptor ligands as well as a method for marking and identifying metabotropic glutamate receptor sites and for imaging an organ.

In the framework of this application, the term "specific" means that the ligand binds
15 preferentially to the mGlu1 receptor site. The term "non-competitive" means that the ligand does not or only marginally displaces glutamate bonded to the mGlu1 receptor site.

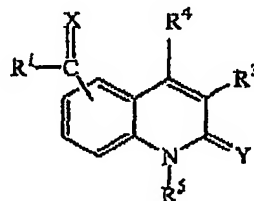
WO 99/26927 discloses antagonists of Group I mGluRs for treating neurological
20 diseases and disorders, based - among others - on a quinoline structure.
WO 99/03822 discloses bicyclic metabotropic glutamate receptor ligands, none of them based on a quinoline or quinolinone structure.

Detailed Description

25 The present invention concerns the radiolabelled compounds of Formula (I-A)* or (I-B)*



(I-A)*

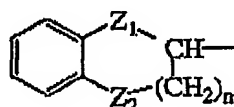


(I-B)*

an N-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine and a
30 stereochemical isomeric form thereof, wherein

X represents O; C(R⁶)₂ with R⁶ being hydrogen, aryl or C₁₋₆alkyl optionally substituted with amino or mono- or di(C₁₋₆alkyl)amino; S or N-R⁷ with R⁷ being amino or hydroxy;

R¹ represents C₁₋₆alkyl; aryl; thienyl; quinoliny; cycloC₃₋₁₂alkyl or (cycloC₃₋₁₂alkyl)C₁₋₆alkyl, wherein the cycloC₃₋₁₂alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC₃₋₁₂alkyl moiety may be replaced by an oxygen atom or an NR⁸-moiety with R⁸ being hydrogen, benzyl or C₁₋₆alkyloxycarbonyl; wherein one or more hydrogen atoms in a C₁₋₆alkyl-moiety or in a cycloC₃₋₁₂alkyl-moiety optionally may be replaced by C₁₋₆alkyl, hydroxyC₁₋₆alkyl, haloC₁₋₆alkyl, aminoC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, arylC₁₋₆alkyloxy, halo, C₁₋₆alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula -O-, -O-CH₂-O or -O-CH₂-CH₂-O-; or a radical of formula (a-1)



a-1

wherein Z₁ is a single covalent bond, O, NH or CH₂;

Z₂ is a single covalent bond, O, NH or CH₂;

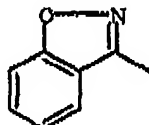
n is an integer of 0, 1, 2 or 3;

and wherein each hydrogen atom in the phenyl ring independently may optionally be replaced by halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy or hydroxyC₁₋₆alkyl;

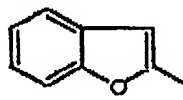
or X and R¹ may be taken together with the carbon atom to which X and R¹ are attached to form a radical of formula (b-1), (b-2) or (b-3);



b-1



b-2



b-3

R² represents hydrogen; halo; cyano; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylthio; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxyC₁₋₆alkyl;

- C₂₋₆alkenyl; hydroxyC₂₋₆alkenyl; C₂₋₆alkynyl; hydroxyC₂₋₆alkynyl;
tri(C₁₋₆alkyl)silaneC₂₋₆alkynyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxyC₁₋₆alkyl)amino; mono- or di(C₁₋₆alkylthioC₁₋₆alkyl)amino; aryl;
arylC₁₋₆alkyl; arylC₂₋₆alkynyl; C₁₋₆alkyloxyC₁₋₆alkylaminoC₁₋₆alkyl;
5 aminocarbonyl optionally substituted with C₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl,
C₁₋₆alkyloxy carbonylC₁₋₆alkyl or pyridinylC₁₋₆alkyl;
a heterocycle selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl,
imidazolyl, isothiazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl,
pyrimidinyl, piperidinyl and piperazinyl, optionally N-substituted with
10 C₁₋₆alkyloxyC₁₋₆alkyl, morpholinyl, thiomorpholinyl, dioxanyl or dithianyl;
a radical -NH-C(=O)R⁹ wherein R⁹ represents
C₁₋₆alkyl optionally substituted with cycloC₃₋₁₂alkyl, C₁₋₆alkyloxy,
C₁₋₆alkyloxy carbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or
di(C₁₋₆alkyl)amino, C₁₋₆alkylthio, benzylthio, pyridinylthio or
15 pyrimidinylthio;
cycloC₃₋₁₂alkyl; cyclohexenyl; amino; arylcycloC₃₋₁₂alkylamino;
mono-or-di(C₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxy carbonylC₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxy carbonyl)amino; mono-or di(C₂₋₆alkenyl)amino; mono- or
20 di(arylC₁₋₆alkyl)amino; mono- or diarylamino; arylC₂₋₆alkenyl;
furanylC₂₋₆alkenyl; piperidinyl; piperazinyl; indolyl; furyl; benzofuryl;
tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl;
arylC₁₋₆alkylthio or a radical of formula (a-1);
a sulfonamid -NH-SO₂-R¹⁰ wherein R¹⁰ represents C₁₋₆alkyl, mono- or poly
25 haloC₁₋₆alkyl, arylC₁₋₆alkyl, arylC₂₋₆alkenyl, aryl, quinolinyl, isoxazolyl
or di(C₁₋₆alkyl)amino;
R³ and R⁴ each independently represent hydrogen; halo; hydroxy; cyano; C₁₋₆alkyl;
C₁₋₆alkyloxy; C₁₋₆alkyloxyC₁₋₆alkyl; C₁₋₆alkyl carbonyl; C₁₋₆alkyloxy carbonyl;
C₂₋₆alkenyl; hydroxyC₂₋₆alkenyl; C₂₋₆alkynyl; hydroxyC₂₋₆alkynyl;
30 tri(C₁₋₆alkyl)silaneC₂₋₆alkynyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxyC₁₋₆alkyl)amino; mono- or di(C₁₋₆alkylthioC₁₋₆alkyl)amino; aryl;
morpholinylC₁₋₆alkyl or piperidinylC₁₋₆alkyl; or
R² and R³ may be taken together to form -R²-R³-, which represents a bivalent radical of
formula -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₆-, -CH=CH-CH=CH-,
35 -Z₄-CH=CH-, -CH=CH-Z₄-, -Z₄-CH₂-CH₂-CH₂-, -CH₂-Z₄-CH₂-CH₂-,
-CH₂-CH₂-Z₄-CH₂-,
-CH₂-CH₂-CH₂-Z₄-, -Z₄-CH₂-CH₂-, -CH₂-Z₄-CH₂- or -CH₂-CH₂-Z₄-, with Z₄ being

O, S, SO₂ or NR¹¹ wherein R¹¹ is hydrogen, C₁₋₆alkyl, benzyl or C₁₋₆alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C₁₋₆alkyl.

or R³ and R⁴ may be taken together to form a bivalent radical of formula

5 -CH=CH-CH=CH- or -CH₂-CH₂-CH₂-CH₂- ;

R⁵ represents hydrogen; cycloC₃₋₁₂alkyl; piperidinyl; oxo-thienyl; tetrahydrothienyl, arylC₁₋₆alkyl; C₁₋₆alkyloxyC₁₋₆alkyl; C₁₋₆alkyloxycarbonylC₁₋₆alkyl or C₁₋₆alkyl optionally substituted with a radical C(=O)NR_xR_y, in which R_x and R_y, each independently are hydrogen, cycloC₃₋₁₂alkyl, C₂₋₆alkynyl or C₁₋₆alkyl optionally substituted with cyano, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, furanyl, pyrrolidinyl, 10 benzylthio, pyridinyl, pyrrolyl or thienyl;

Y represents O or S;

or Y and R⁵ may be taken together to form =Y-R⁵- which represents a radical of formula

15 -CH=N-N= (c-1);
 -N=N-N= (c-2); or
 -N-CH=CH- (c-3);

aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, phenyloxy, nitro, amino, thio, 20 C₁₋₆alkylthio, haloC₁₋₆alkyl, polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono-or di(C₁₋₆alkyl)amino; mono-or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, cyano, -CO-R¹², -CO-OR¹³, -NR¹³SO₂R¹², -SO₂-NR¹³R¹⁴, -NR¹³C(O)R¹², -C(O)NR¹³R¹⁴, -SOR¹², -SO₂R¹²; wherein each R¹², R¹³ and R¹⁴ independently represent C₁₋₆alkyl; 25 cycloC₃₋₆alkyl; phenyl; phenyl substituted with halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, haloC₁₋₆alkyl, polyhaloC₁₋₆alkyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl or oxazolyl;

and when the R¹-C(=X) moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R¹⁵ and R¹⁶ wherein either one or

30 both of R¹⁵ and R¹⁶ represents C₁₋₆alkyl, C₁₋₆alkyloxy or R¹⁵ and R¹⁶ taken together may form a bivalent radical of formula -CH=CH-CH=CH-.

As used in the foregoing definitions and hereinafter C₁₋₆alkyl as a group or part of a group encompasses the straight and branched chain saturated hydrocarbon radicals 35 having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl; C₂₋₆alkenyl as a group or part of a group encompasses the straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms and having a

- double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl, 3-methylbutenyl and the like; C_{2-6} alkynyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 2 to 6 carbon atoms and having a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, 3-methylbutynyl and the like;
- 5 $cycloC_{3-6}$ alkyl encompasses monocyclic alkyl ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl; $cycloC_{3-12}$ alkyl encompasses mono-, bi- or tricyclic alkyl ring structures and is generic to for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornanyl, adamantyl.
- 10 The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalo C_{1-6} alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6} alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are
- 15 attached to an alkyl group within the definition of polyhalo C_{1-6} alkyl, they may be the same or different.

When any variable, e.g. aryl, occurs more than one time in any constituent, each definition is independent.

- 20 When any bond is drawn into a ring structure, it means that the corresponding substituent may be linked to any atom of said ring structure. This means for instance that the $R^1-C(=X)$ moiety may be linked to the quinoline or quinolinone moiety in position 5, 6, 7, 8 but also position 3 or position 4.
- 25 By the term "radiolabelled compound" is meant any compound according to Formula (I-A)* or (I-B)*, an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine or a stereochemically isomeric form thereof, which contains at least one radioactive atom. In the framework of this application, compounds which do not contain a radio-active atom are denoted without an asterisk to their formula number,
- 30 compounds which contain a radio-active atom are denoted with an asterisk to their formula number.

- In particular, the radioactive atom is selected from the group of hydrogen, carbon, nitrogen, sulfur, oxygen and halogen. Preferably, the radioactive atom is selected from
- 35 the group of hydrogen, carbon and halogen.

In particular, the radioactive atom is selected from the group of ^3H , ^{11}C , ^{18}F , ^{122}I , ^{123}I , ^{125}I , ^{131}I , ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br . Preferably, the radioactive atom is selected from the group of ^3H , ^{11}C and ^{18}F .

- 5 By the term "compound according to the invention" is meant a compound according to Formula (I-A)* or (I-B)*, an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

- For *in vivo* use, salts of the compounds of Formula (I-A)* and (I-B)* are those wherein
10 the counter ion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention. With the term "in vivo" is meant any use of the compounds according to the
15 invention whereby said compounds are administered to live animals.

- The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of Formula (I-A)* and (I-B)* are able to form. The latter can conveniently
20 be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic,
25 methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

- 30 The compounds of Formula (I-A)* and (I-B)* containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with
35 organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine,

diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term "addition salt" also comprises the hydrates and solvent addition forms which the compounds of Formula (I-A)* and (I-B)* are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of Formula (I-A)* and (I-B)* are able to form by reaction between a basic nitrogen of a compound of Formula (I-A)* or (I-B)* and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counter ions include chloro, bromo, iodo, trifluoroacetate and acetate. The counter ion of choice can be introduced using ion exchange resins.

It will be appreciated that some of the compounds according to the invention may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds according to the invention or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereoisomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of the compounds according to the invention, substantially free, i.e. associated with less than 10 %, preferably less than 5 %, in particular less than 2% and most preferably less than 1 % of the other isomers. Stereochemically isomeric forms of the compounds according to the invention are obviously intended to be embraced within the scope of the present invention. The same applies to the intermediates as described herein, used to prepare end products of the compounds according to the invention.

The terms *cis* and *trans* are used herein in accordance with Chemical Abstracts nomenclature.

- 5 In some compounds according to the invention and in the intermediates used in their preparation, the absolute stereochemical configuration has not been determined. In these cases, the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized
10 by physicochemical characteristics such as their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1"
15 and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

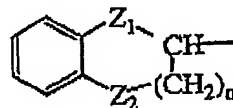
The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I-A)* and (I-B)* wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.
20

Some of the compounds according to the invention may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. Of special interest are those
25 compounds of formula (I-A)* and (I-B)* which are stereochemically pure.

An interesting group of compounds are those compounds of formula (I-A)* and (I-B)* wherein

- X represents O; C(R⁶)₂ with R⁶ being hydrogen or aryl ; or N-R⁷ with R⁷ being amino
30 or hydroxy;
R¹ represents C₁₋₆alkyl, aryl; thienyl; quinoliny; cycloC₃₋₁₂alkyl or (cycloC₃₋₁₂alkyl)C₁₋₆alkyl, wherein the cycloC₃₋₁₂alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC₃₋₁₂alkyl moiety may be replaced by an oxygen atom or an NR⁸-moiety with R⁸ being benzyl or
35 C₁₋₆alkyloxycarbonyl ; wherein one or more hydrogen atoms in a C₁₋₆alkyl-moiety or in a cycloC₃₋₁₂alkyl-moiety optionally may be replaced by C₁₋₆alkyl, haloC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, arylC₁₋₆alkyloxy, halo, aryl, mono- or

di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula -O- or -O-CH₂-CH₂-O-; or a radical of formula (a-1)



a-1

wherein Z₁ is a single covalent bond, O or CH₂;

Z₂ is a single covalent bond, O or CH₂;

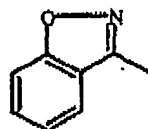
n is an integer of 0, 1, or 2 ;

and wherein each hydrogen atom in the phenyl ring independently may optionally be replaced by halo or hydroxy;

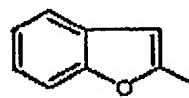
or X and R¹ may be taken together with the carbon atom to which X and R¹ are attached to form a radical of formula (b-1), (b-2) or (b-3);



b-1



b-2



b-3

R² represents hydrogen; halo; cyano; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylthio; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₂₋₆alkenyl; hydroxyC₂₋₆alkenyl; C₂₋₆alkynyl; hydroxyC₂₋₆alkynyl; tri(C₁₋₆alkyl)silaneC₂₋₆alkynyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyloxyC₁₋₆alkyl)amino; mono- or di(C₁₋₆alkylthioC₁₋₆alkyl)amino; aryl; arylC₁₋₆alkyl; arylC₂₋₆alkynyl; C₁₋₆alkyloxyC₁₋₆alkylaminoC₁₋₆alkyl; aminocarbonyl optionally substituted with C₁₋₆alkyloxycarbonylC₁₋₆alkyl ; a heterocycle selected from thienyl, furanyl, thiazolyl and piperidinyl, optionally N-substituted with morpholinyl or thiomorpholinyl; a radical -NH-C(=O)R⁹ wherein R⁹ represents C₁₋₆alkyl optionally substituted with cycloC₃₋₁₂alkyl, C₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylthio, benzylthio, pyridinylthio or pyrimidinylthio; cycloC₃₋₁₂alkyl; cyclohexenyl; amino; arylcycloC₃₋₁₂alkylamino; mono-or-di(C₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyloxycarbonylC₁₋₆alkyl)amino; mono- or di(C₁₋₆alkyloxycarbonyl)amino; mono-or di(C₂₋₆alkenyl)amino; mono- or

- di(arylC₁₋₆alkyl)amino; mono- or diarylamino; arylC₂₋₆alkenyl; furanylC₂₋₆alkenyl; piperididynyl; piperazinyl; indolyl; furyl; benzofuryl; tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl or a radical of formula (a-1) ;
a sulfonamid -NH-SO₂-R¹⁰ wherein R¹⁰ represents C₁₋₆alkyl, mono- or poly
- 5 haloC₁₋₆alkyl, arylC₁₋₆alkyl or aryl;
R³ and R⁴ each independently represent hydrogen; C₁₋₆alkyl; C₁₋₆alkyloxyC₁₋₆alkyl; C₁₋₆alkyloxycarbonyl; or
R² and R³ may be taken together to form -R²-R³-, which represents a bivalent radical of formula -(CH₂)₄-, -(CH₂)₅-, -Z₄-CH=CH-, -Z₄-CH₂-CH₂-CH₂- or -Z₄-CH₂-CH₂-,
10 with Z₄ being O, S, SO₂ or NR¹¹ wherein R¹¹ is hydrogen, C₁₋₆alkyl, benzyl or C₁₋₆alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C₁₋₆alkyl;
or R³ and R⁴ may be taken together to form a bivalent radical of formula
-CH=CH-CH=CH- or -CH₂-CH₂-CH₂-CH₂- ;
- 15 R⁵ represents hydrogen; piperidinyl; oxo-thienyl; tetrahydrothienyl, arylC₁₋₆alkyl; C₁₋₆alkyloxycarbonylC₁₋₆alkyl or C₁₋₆alkyl optionally substituted with a radical C(=O)NR_xR_y, in which R_x and R_y, each independently are hydrogen, cycloC₃₋₁₂alkyl, C₂₋₆alkynyl or C₁₋₆alkyl optionally substituted with cyano, C₁₋₆alkyloxy or C₁₋₆alkyloxycarbonyl;
- 20 Y represents O or S;
or Y and R⁵ may be taken together to form =Y-R⁵- which represents a radical of formula
-CH=N-N= (c-1); or
-N=N-N= (c-2);
- 25 aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, C₁₋₆alkyloxy, phenyloxy, mono-or di(C₁₋₆alkyl)amino and cyano;
and when the R¹-C(=X) moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R¹⁵ and R¹⁶ wherein either one or
30 both of R¹⁵ and R¹⁶ represents C₁₋₆alkyl or R¹⁵ and R¹⁶ taken together may form a bivalent radical of formula -CH=CH-CH=CH-.

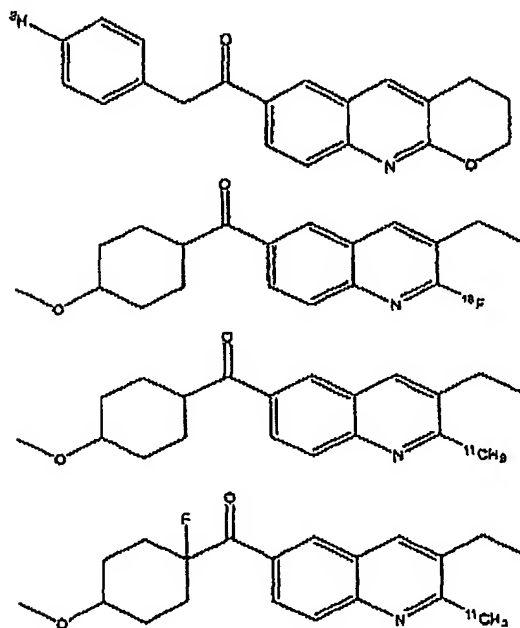
A further most interesting group of compounds comprises those compounds of formula (I-A)* and (I-B)* wherein X represents O;

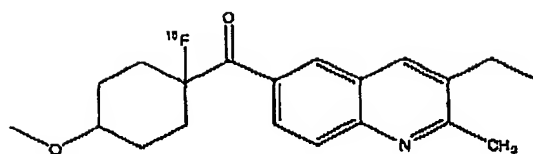
- 35 R¹ represents C₁₋₆alkyl; cycloC₃₋₁₂alkyl or (cycloC₃₋₁₂alkyl)C₁₋₆alkyl, wherein one or more hydrogen atoms in a C₁₋₆alkyl-moiety or in a cycloC₃₋₁₂alkyl-moiety optionally may be replaced by C₁₋₆alkyloxy, aryl, halo or thienyl;

- R^2 represents hydrogen; halo; C_{1-6} alkyl or amino;
 R^3 and R^4 each independently represent hydrogen or C_{1-6} alkyl; or
 R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of
 formula $-Z_4-CH_2-CH_2-CH_2-$ or $-Z_4-CH_2-CH_2-$ with Z_4 being O or NR^{11} wherein
 5 R^{11} is C_{1-6} alkyl; and wherein each bivalent radical is optionally substituted with
 C_{1-6} alkyl;
 or R^3 and R^4 may be taken together to form a bivalent radical of formula
 $-CH_2-CH_2-CH_2-CH_2-$;
 R^5 represents hydrogen;
 10 Y represents O; and
 aryl represents phenyl optionally substituted with halo.

- A further interesting group of compounds comprises those compounds of formula
 (I-A)* and (I-B)* wherein the $R^1-C(=X)$ moiety is linked to the quinoline or
 15 quinolinone moiety in position 6.

Especially interesting are the following radioactive compounds :





All compounds according to the invention show a moderate to strong mGluR1 activity. Such activity is among others attributed to the specific binding of said compound to the mGlu1 receptor, which makes the compounds useful in a diagnostic method, e.g. for labeling and detecting mGlu1 receptor sites. The invention therefore also relates to a radiolabelled compound according to the invention for use in a diagnostic method.

First preferred embodiment

According to a first preferred embodiment, the radiolabelled compound comprises at least one [^3H]-atom or one [^{125}I]-atom. A [^3H]-atom is conveniently introduced by partially or completely substituting one or more non-radioactive [^1H]-hydrogen atoms in the molecule by their radioactive isotopes. The choice of whether a [^3H] or [^{125}I] radioligand will be used may depend in part on the availability of liquid scintillation counters (LSC), which are fairly expensive. [^{125}I] ligands can be quantified using either a γ -counter or an LSC, whereas [^3H] ligands necessitate the use of an LSC.

The radiolabelled compound comprising at least one [^3H]-atom or one [^{125}I]-atom is advantageously used in radioligand-binding techniques, in particular in *in vitro* membrane receptor assays for marking or identifying a mGlu1 receptor in biological material.

The radiolabelled compounds comprising at least one [^3H]-atom or one [^{125}I]-atom is also advantageously used in *in vivo* mGlu1 receptor autoradiography of the brain since the compounds according to the invention have the advantageous and unexpected ability to readily cross the blood-brain barrier.

The invention therefore also relates to a radiolabelled compound according to the invention used in a diagnostic method which consists of marking or identifying a mGlu1 receptor in biological material, as well as the use of the compounds according to the invention for the manufacture of a diagnostic tool for marking or identifying an mGlu1 receptor in biological material, whether *in vivo* or *in vitro*.

In the framework of this application, by the term "biological material" is meant to include any material which has a biological origin. In particular, this relates to tissue samples, plasma fluids, body fluids, body parts and organs originating from warm-blooded animals and warm-blooded animals *per se*, in particular humans.

5

Basic experiments that are performed using the membrane assay system for marking or identifying a mGlu1 receptor in biological material are : saturation experiments, inhibition experiments, association kinetic experiments and dissociation kinetic experiments. These methods are applicable to most neurotransmitter and hormone
10 receptor systems, including the mGluR1-system (Methods for Neurotransmitter Receptor Analysis, ed. by Henry I. Yamamura et al., Raven Press Ltd., New York, 1990). To this end, the radiolabelled compound is administered to the biological material to mark the mGlu1 receptors and the emissions from the radiolabelled compound are detected to identify the amount or location of the mGlu1 receptors, for
15 instance for *ex vivo* receptor autoradiography.

The radiolabelled compounds according to the invention comprising at least one [^3H]-atom or one [^{125}I]-atom are also useful as agents for screening whether a test
20 compound has the ability to occupy or bind to a mGlu1 receptor site. The degree to which a test compound will displace a compound according to the invention from the mGlu1 receptor site will show the test compound ability to occupy or bind to a mGluR1 receptor and therefore act as either an agonist, an antagonist or a mixed agonist/antagonist of a mGlu1 receptor.

25 The radiolabelled compounds according to the invention comprising at least one [^3H]-atom or one [^{125}I]-atom are advantageously prepared by substituting a halogen atom with a tritium atom, as is documented in the Experimental Section below.

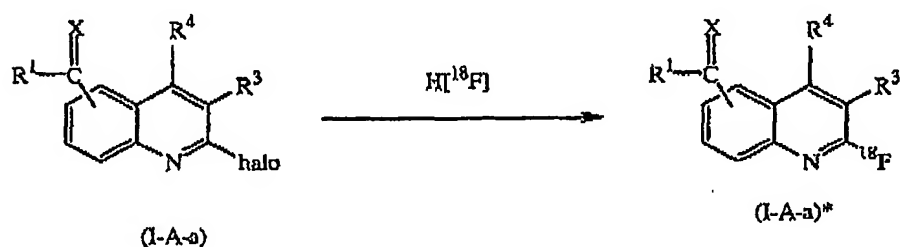
Second Preferred Embodiment

30 In a second preferred embodiment, the radiolabelled compound comprises at least one radioactive carbon or halogen atom. In principle, any compound according to Formula (I) containing a carbon or halogen atom is prone for radiolabel ling by replacing the carbon or halogen atom by a suitable radioactive isotope or by making the compounds according to Formula (I) using radioactively-labelled reagentia. Suitable halogen
35 radioisotopes to this purpose are radioactive carbon, e.g. [^{14}C] ; radioactive iodides, e.g. [^{122}I], [^{123}I], [^{131}I] ; radioactive bromides, e.g. [^{75}Br], [^{76}Br], [^{77}Br] and [^{82}Br] ; and radioactive fluorides, e.g. [^{18}F]. Preferred radiolabelled compounds are those

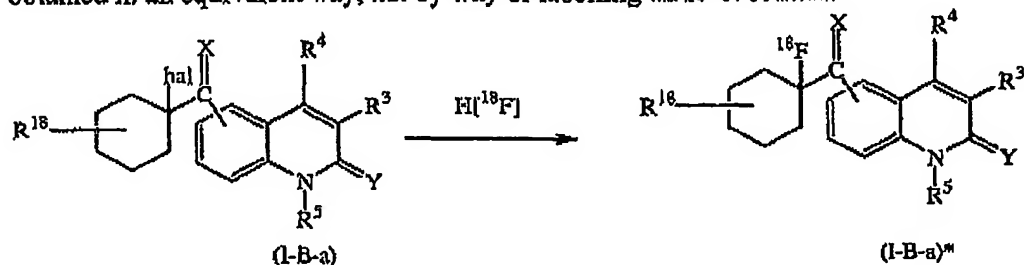
compounds of Formula (I-A)* and (I-B)*, wherein R^1 is a radioactive carbon or halo atom, especially [^{11}C], [^{18}F], [^{123}I], [^{75}Br], [^{76}Br] or [^{77}Br].

Preparation of the radioactive compounds

- 5 The introduction of a radioactive halogen atom can be performed by a suitable reaction such as depicted below

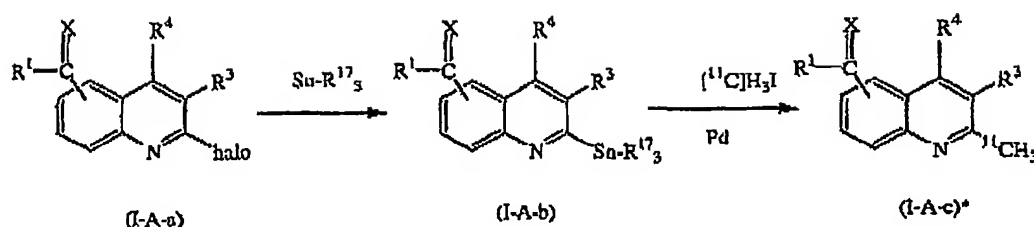


- 10 in which all substituents in Formula (I-A-a) and (I-A-a)* are defined as in Formula (I-A)* and halo is a halogen atom. A suitable compound (I-A-a) is reacted with $\text{H}[^{18}\text{F}]$ such that the halogen atom present on the quinoline ring is displaced by a nucleophilic displacement reaction with the radioactive [^{18}F] atom.
- 15 For obtaining radiolabelled compounds according to Formula (I-B)*, radiolabelling can be performed on an equivalent way, for instance by way of a reaction scheme as depicted below. Obviously, also compounds according to Formula (I-A)* can be obtained in an equivalent way, i.e. by way of labelling an R^1 substituent.



- 20 The introduction of a radioactive [^{11}C] can be performed using the reaction scheme below in which a suitable compound (I-A-a) is first stannylated after which the radioactive [^{11}C] is introduced using e.g. a palladium catalyzed "Stille-type" coupling reaction using [^{11}C]methyl iodide (Scott, W.J.; Crisp, G.T.; Stille, J.K. *J. Am. Chem. Soc.*, 1984, 106, 4630).

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In Formula (I-A-a), (I-A-b) and (I-A-c)*, all substituents have the same meaning as defined in Formula (I-A)*, halo is a halogen atom and R¹⁷ is methyl or butyl.

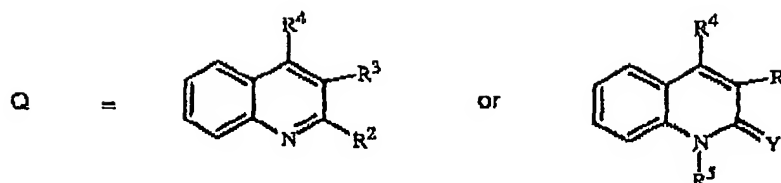
Because of their unexpected property to penetrate readily the blood-brain barrier, the radiolabelled compounds comprising a radioactive halogen atom are advantageously administered *in vivo*, in an appropriate composition to an animal, especially a warm-blooded animal, and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computered Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of mGlu1 receptor sites throughout the body can be detected and organs containing mGlu1 receptor sites such as, for example, the brain, can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of Formula (I-A)* or (I-B)*, which bind to the mGlu1 receptor sites and detecting the emissions from the radioactive compound also constitutes an aspect of the present invention.

The application of the compounds of Formula (I-A)* and (I-B)* in the above described techniques constitutes a further aspect of the present invention. The invention in particular relates to the use of the compounds according to the invention for the manufacture of a diagnostic tool for use in PET. For use in PET, most preferred are radiolabelled compounds according to the invention, in which a ¹⁸F is incorporated (US 4,931,270 by Horn et al., published June 5, 1990).

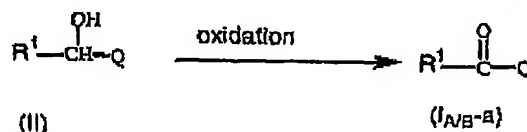
Preparation of the non-radioactive compounds

The non-radioactive compounds according to the invention may be produced in a number of ways.

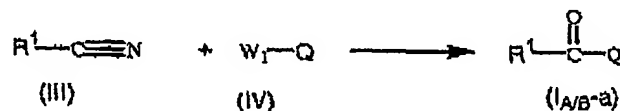
In order to simplify the structural representation of some of the present compounds and intermediates in the following preparation procedures, the quinoline or the quinolinone moiety will hereinafter be represented by the symbol Q.



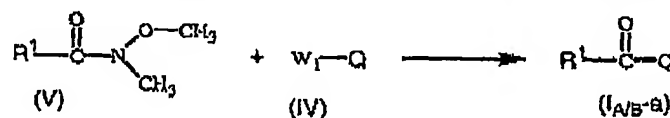
The compounds of formula (I-A) or (I-B), wherein X represents O, said compounds being represented by formula (I_{A/B-a}), can be prepared by oxidizing an intermediate of formula (II) in the presence of a suitable oxidizing agent, such as potassium permanganate, and a suitable phase-transfer catalyst, such as tri(dioxa-3,6-heptyl)amine, in a suitable reaction-inert solvent, such as for example dichloromethane.



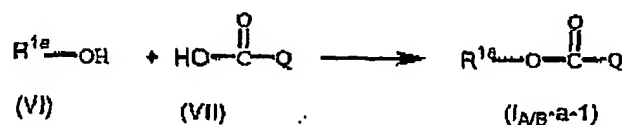
Compounds of formula (I_{A/B-a}) may also be prepared by reacting an intermediate of formula (III) with an intermediate of formula (IV), wherein W₁ represents a halo atom, e.g. bromo, in the presence of butyl lithium and a suitable reaction-inert solvent, such as for example tetrahydrofuran.



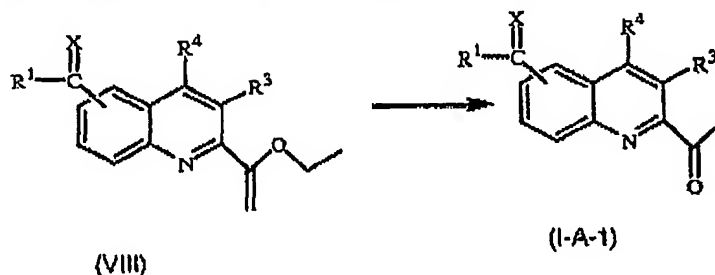
Alternatively, compounds of formula (I_{A/B-a}) may also be prepared by reacting an intermediate of formula (V) with an intermediate of formula (IV) in the presence of butyl lithium and a suitable reaction-inert solvent, such as for example tetrahydrofuran.



Compounds of formula (I_{A/B-a}), wherein the R¹ substituent is linked to the carbonyl moiety via an oxygen atom, said R¹ substituent being represented by O-R^{1a} and said compounds by formula (I_{A/B-a-1}), can be prepared by reacting an intermediate of formula (VI) with an intermediate of formula (VII) in the presence of a suitable acid, such as sulfuric acid.



Compounds of formula (I-A), wherein R^2 represents methylcarbonyl, said compounds being represented by formula (I-A-1), can be prepared by reacting an intermediate of formula (VIII) in the presence of a suitable acid, such as hydrochloric acid, and a suitable reaction-inert solvent, such as for example tetrahydrofuran.



5

The compounds of formula (I) may also be converted into each other following art-known transformations.

Compounds of formula (I-A) wherein R^2 is a halo atom, such as chloro, can be converted into a compound of formula (I-A), wherein R^2 is another halo atom, such as fluoro or iodo, by reaction with a suitable halogenating agent, such as for example potassium fluoride or sodium iodide, in the presence of a suitable reaction-inert solvent, e.g. dimethyl sulfoxide or acetonitrile and optionally in the presence of acetyl chloride.

Compounds of formula (I-A), wherein R^2 is a suitable leaving group, such as a halo atom, e.g. chloro, iodo, said leaving group being represented by W^2 and said compounds by (I-A-2), can be converted into a compound of formula (I-A) wherein R^2 is cyano, said compound being represented by formula (I-A-3), by reaction with a suitable cyano-introducing agent, such as for example trimethylsilanecarbonitrile, in the presence of a suitable base such as *N,N*-diethylethanamine and a suitable catalyst, such as for example tetrakis(triphenylphosphine)palladium.

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A-4) by reaction with C_{2-6} alkynyltri(C_{1-6} alkyl)silane in the presence of CuI, an appropriate base, such as for example *N,N*-diethylethanamine, and an appropriate catalyst, such as for example tetrakis(triphenylphosphine)palladium. Compounds of formula (I-A-4) can on their turn be converted into a compound of formula (I-A-5) by reaction with potassium fluoride in the presence of a suitable acid such as acetic acid, or by reaction with a suitable base, such as potassium hydroxide, in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.

30

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A-6) by reaction with an intermediate of formula (IX) in the presence of CuI, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable catalyst such as tetrakis(triphenylphosphine)palladium.

5

Compounds of formula (I-A-2) can also be converted into a compound wherein R^2 is C_{1-6} alkyl, said compound being represented by formula (I-A-8) in the presence of a suitable alkylating agent, such as for example $Sn(C_{1-6}alkyl)_4$, or into a compound wherein R^2 is C_{2-6} alkenyl, said compound being represented by formula (I-A-9) in the presence of a suitable alkenylating agent, such as for example $Sn(C_{2-6}alkenyl)(C_{1-6}alkyl)_3$, both reactions in the presence of a suitable catalyst, such as for example tetrakis(triphenylphosphine)palladium and a reaction-inert solvent, such as for example toluene or dioxane.

15 Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A-7) wherein Z represents O or S, by reaction with an intermediate of formula (X) optionally in the presence of a suitable base such as dipotassium carbonate and a reaction-inert solvent, such as *N,N*-dimethyl formamide.

20 Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A), wherein R^2 is C_{1-6} alkyloxycarbonyl, said compound being represented by formula (I-A-10) and a compound of formula (I-A), wherein R^2 is hydrogen, said compound being represented by formula (I-A-11), by reaction with a suitable alcohol of formula

25 $C_{1-6}alkylOH$ and CO in the presence of a suitable catalyst, such as for example palladium(II)acetate, triphenylphosphine, a suitable base such as dipotassium carbonate and a reaction-inert solvent, such as *N,N*-dimethylformamide.

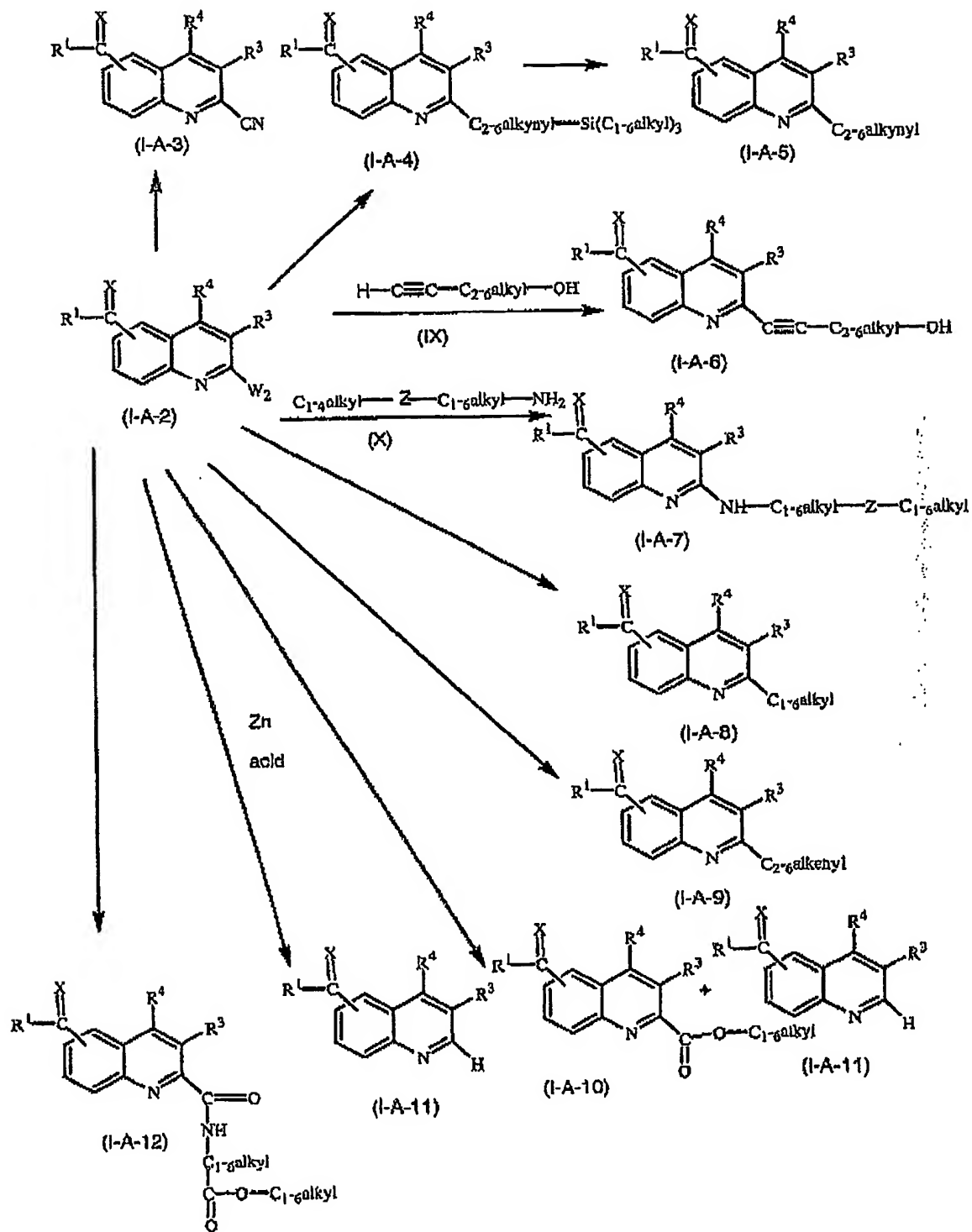
30 Compounds of formula (I-A-11) can also be prepared by reacting a compound of formula (I-A-2) with Zn in the presence of a suitable acid such as acetic acid.

Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A), wherein R^2 is aminocarbonyl substituted with C_{1-6} alkyloxycarbonyl $C_{1-6}alkyl$, said compound being represented by formula (I-A-12), by reaction with an intermediate of formula $H_2N-C_{1-6}alkyl-C(=O)-O-C_{1-6}alkyl$ in the presence of CO, a suitable catalyst such as tetrakis(triphenylphosphine)palladium, a suitable base, such as for example

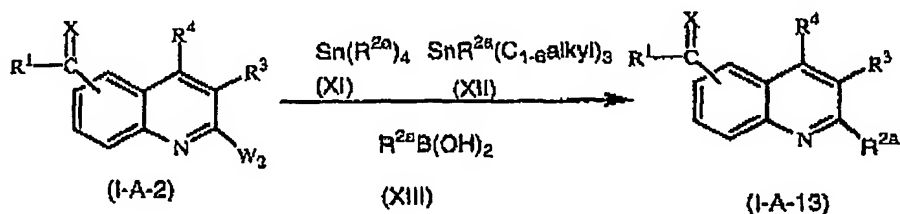
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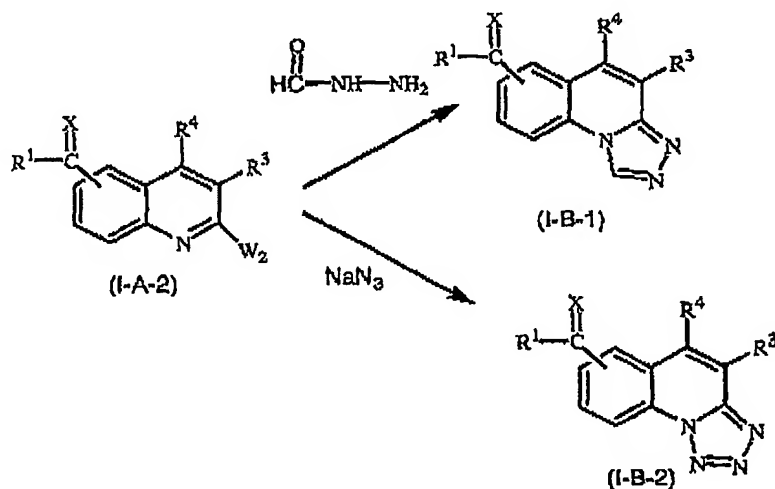
N,N-diethylethanamine, and a suitable reaction-inert solvent, such as for example toluene.



- Compounds of formula (I-A-2) can also be converted into a compound of formula (I-A) wherein R^2 is aryl or a heterocycle selected from the group described in the definition of R^2 hereinabove, said R^2 being represented by R^{2a} and said compound by formula (I-A-13) by reaction with an intermediate of formula (XI), (XII) or (XIII) in the presence of a suitable catalyst such as for example tetrakis(triphenylphosphine)palladium and a suitable reaction-inert solvent, such as for example dioxane.

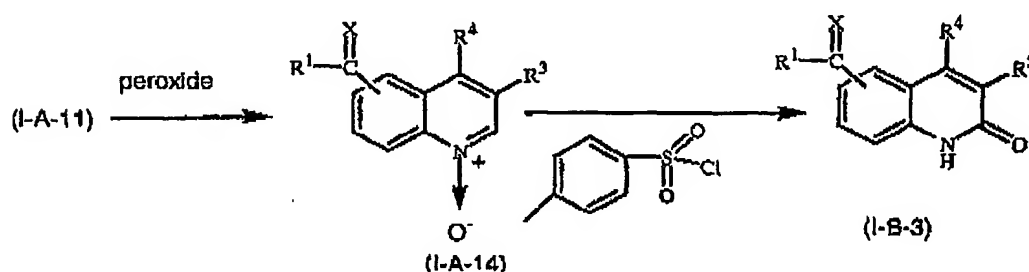


- Compounds of formula (I-A-2) can also be converted into a compound of formula (I-B), wherein Y and R^5 are taken together to form a radical of formula (b-1) or (b-2), said compound being represented by formula (I-B-1) or (I-B-2), by reaction with hydrazinecarboxaldehyde or sodium azide in a suitable reaction-inert solvent, such as an alcohol, e.g. butanol, or *N,N*-dimethylformamide.

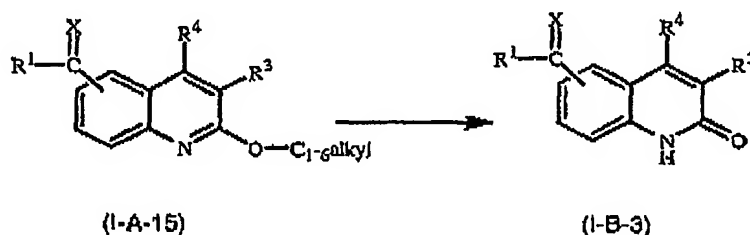


- Compounds of formula (I-A-11) can be converted into the corresponding N-oxide, represented by formula (I-A-14), by reaction with a suitable peroxide, such as 3-chloro-benzenecarboxoperoxoic acid, in a suitable reaction-inert solvent, such as for

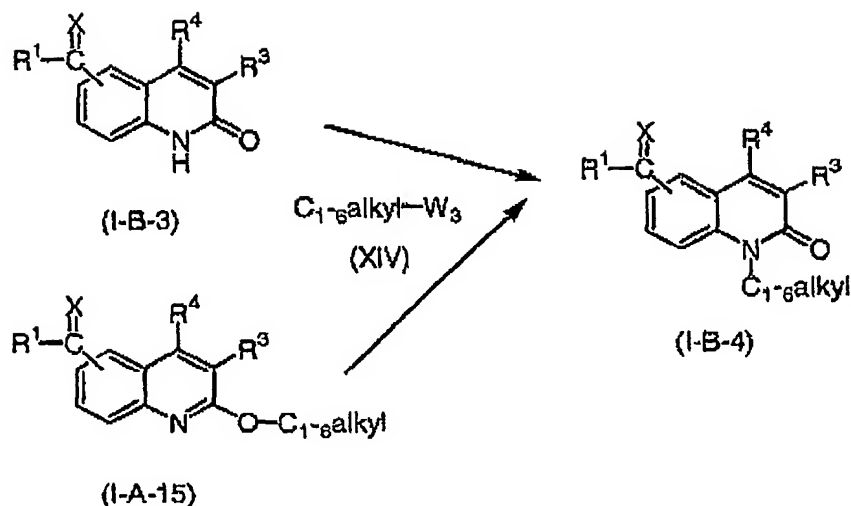
example methylene chloride. Said compound of formula (I-A-14) can further be converted into a compound of formula (I-B), wherein R^5 is hydrogen, said compound being represented by formula (I-B-3), by reaction with 4-methyl-benzene sulfonyl chloride in the presence of a suitable base, such as for example dipotassium carbonate and a suitable reaction-inert solvent, such as for example methylene chloride.



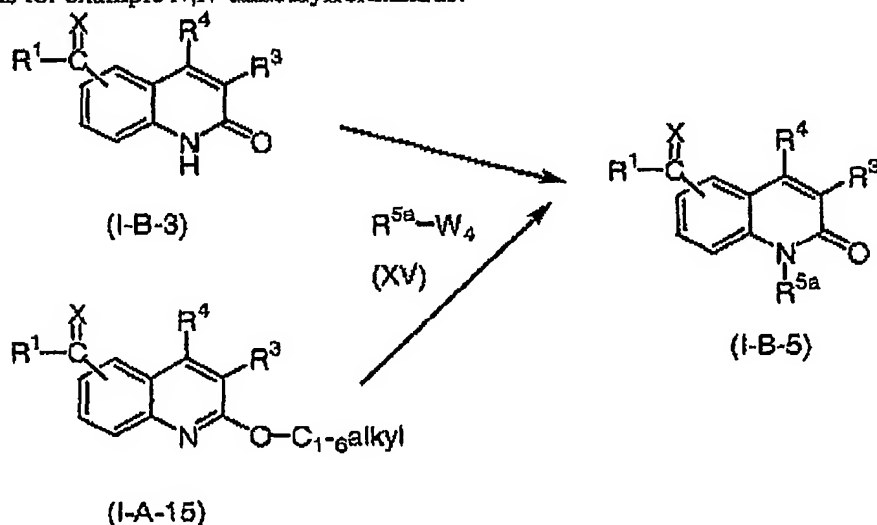
Compounds of formula (I-B-3) can also be prepared from a compound of formula (I-A), wherein R^2 is C_{1-6} alkyloxy, said compound being represented by formula (I-A-15), by reaction with a suitable acid, such as hydrochloric acid, in the presence of a suitable reaction-inert solvent, such as for example tetrahydrofuran.



Compounds of formula (I-B-3) can be converted into a compound of formula (I-B), wherein R^5 represents C_{1-6} alkyl, said compound being represented by formula (I-B-4), by reaction with an appropriate alkylating agent, such as for example an intermediate of formula (XIV), wherein W_3 represents a suitable leaving group such as a halo atom e.g. iodo, in the presence of potassium tert. butoxide and in the presence of a suitable reaction-inert solvent, such as for example tetrahydrofuran.

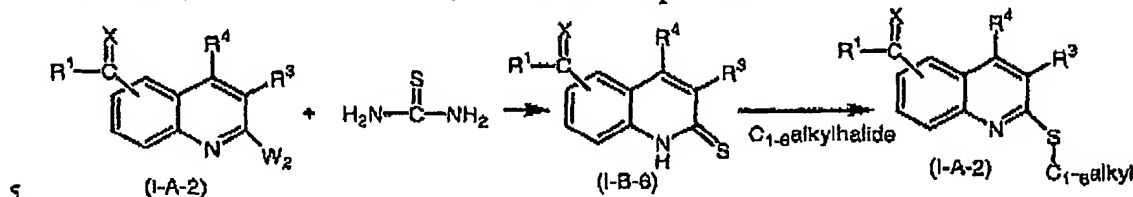


- Compounds of formula (I-B-3) can also be converted into a compound of formula (I-B), wherein R^5 is $C_{1-6}alkyloxycarbonylC_{1-6}alkyl$ or $arylC_{1-6}alkyl$, said R^5 being represented by R^{5a} and said compound being represented by formula (I-B-5), by
- 5 reaction with an intermediate of formula (XV), wherein W_4 represents a suitable leaving group, such as a halo atom, e.g. bromo, chloro and the like, in the presence of a suitable base, such as for example sodium hydride and a suitable reaction-inert solvent, such as for example *N,N*-dimethylformamide.



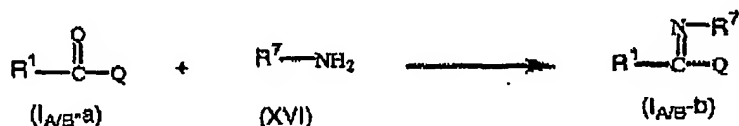
- 10 Compounds of formula (I-A-2) can also be converted into a compound of formula (I-B), wherein R^5 is hydrogen and Y is S , said compound being represented by formula (I-B-6), by reaction with $H_2N-C(=S)-NH_2$ in the presence of a suitable base, such as potassium hydroxide, and a suitable reaction-inert solvent, such as an alcohol, for example ethanol, or water. Compounds of formula (I-B-6) can further be converted

into a compound of formula (I-A), wherein R^2 is C_{1-6} alkylthio, said compound being represented by formula (I-A-16), by reaction with a suitable C_{1-6} alkylhalide, such as for example C_{1-6} alkyliodide, in the presence of a suitable base, such as dipotassium carbonate, and a suitable solvent, such as for example acetone.



Compounds of formula (I_{A/B}-a) can be converted into a compounds of formula (I-A) or (I-B), wherein X is $N-R^7$, said compound being represented by formula (I_{A/B}-b), by reaction with an intermediate of formula (XVI), optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine, and in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. ethanol.

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As already indicated in the preparation procedure of compounds of formula (I-A-13) described above, the compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

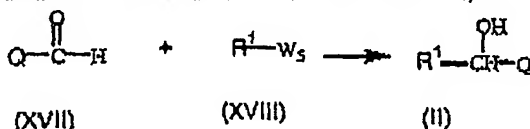
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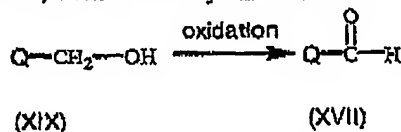
Some of the intermediates and starting materials used in the above reaction procedures are commercially available, or may be synthesized according to procedures already described in the literature.

Intermediates of formula (II) may be prepared by reacting an intermediate of formula (XVII) with an intermediate of formula (XVIII), wherein W_5 represents a suitable leaving group such as a halo atom, e.g. chloro, bromo and the like, in the presence of magnesium, diethylether and a suitable reaction-inert solvent, such as diethylether.



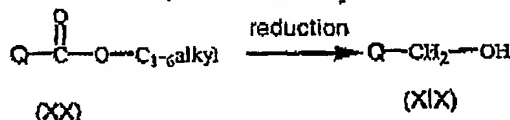
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Intermediates of formula (XVII) may be prepared by oxidizing an intermediate of formula (XIX) in the presence of a suitable oxidizing agent, such as MnO_2 , and a suitable reaction-inert solvent, such as methylene chloride.



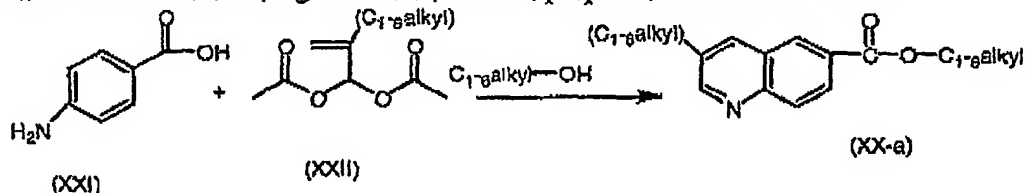
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Intermediates of formula (XIX) can be prepared by reducing an intermediate of formula (XX) in the presence of a suitable reducing agent such as lithium aluminium hydride, and a suitable reaction-inert solvent, such as tetrahydrofuran.



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Intermediates of formula (XX), wherein Q represents a quinoline moiety optionally substituted in position 3 with $\text{C}_{1-6}\text{alkyl}$ and wherein the carbonyl moiety is placed in position 6, said intermediates being represented by formula (XX-a), can be prepared by reacting an intermediate of formula (XXI) with an intermediate of formula (XXII) in the presence of sodium 3-nitro-benzene sulfonate, a suitable acid, such as sulfuric acid, and a suitable alcohol, e.g. methanol, ethanol, propanol, butanol and the like.

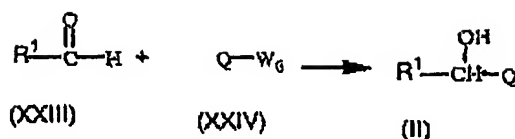


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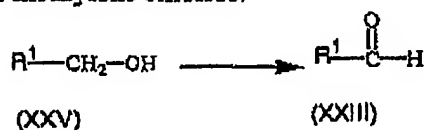
Alternatively, intermediates of formula (II) can also be prepared by reacting an intermediate of formula (XXIII) with an intermediate of formula (XXIV), wherein W_6 is a suitable leaving group, such as a halo atom, e.g. bromo, chloro and the like, in the presence of a suitable agent, such as butyl lithium and a suitable reaction-inert solvent,

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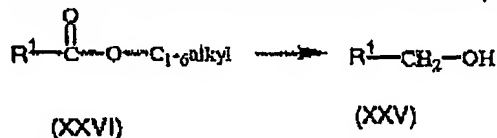
such as tetrahydrofuran.



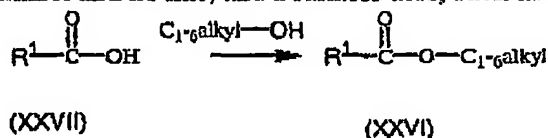
Intermediates of formula (XXIII) can be prepared by oxidizing an intermediate of formula (XXV) using the Moffatt Pfitzner or Swern oxidation (dimethylsulfoxide adducts with dehydrating agents e.g. DCC, Ac₂O, SO₃, P₄O₁₀, COCl₂ or Cl-CO-COCl) in an inert solvent such as methylene chloride.



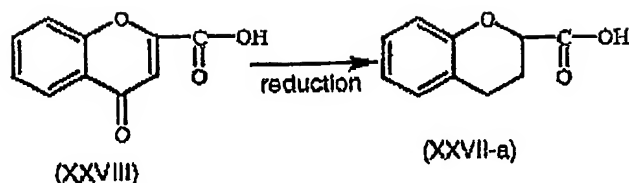
Intermediates of formula (XXV) can be prepared by reducing an intermediate of formula (XXVI) in the presence of a suitable reducing agent, such as for example lithium aluminium hydride and a suitable reaction-inert solvent, such as benzene.



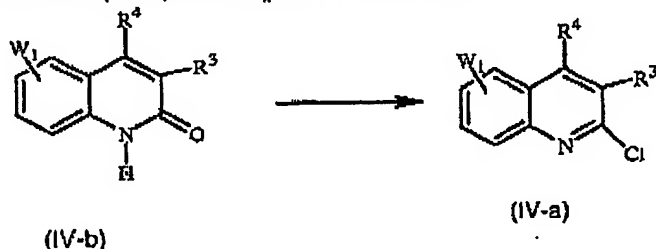
Intermediates of formula (XXVI) can be prepared from an intermediate of formula (XXVII) by esterification in the presence of a suitable alcohol, such as methanol, ethanol, propanol, butanol and he like, and a suitable acid, such as sulfuric acid.



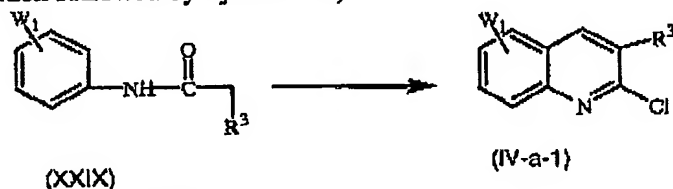
Intermediates of formula (XXVII), wherein R¹ represents a radical of formula (a-1) with Z₁ being O, Z₂ being CH₂ and n being 1, said intermediates being represented by formula (XXVII-a), can be prepared by reducing an intermediate of formula (XXVIII) in the presence of a suitable reducing agent such as hydrogen, and a suitable catalyst, such as palladium on charcoal, and a suitable acid such as acetic acid. When R¹ of intermediate (XXVII) represents an optionally substituted phenyl moiety, it can also be converted into an optionally substituted cyclohexyl moiety by reduction in the presence of a suitable reducing agent such as rhodium on Al₂O₃, and a suitable reaction-inert solvent, such as tetrahydrofuran.



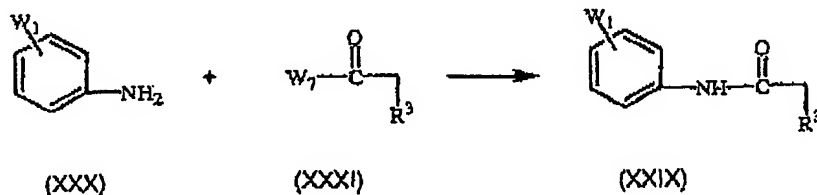
Intermediates of formula (IV), wherein Q represents a quinoline moiety substituted in position 2 with halo, e.g. chloro, said intermediates being represented by formula (IV-a), can be prepared by reacting an intermediate of formula (IV), wherein Q represents a quinolinone moiety with R⁵ being hydrogen, said intermediate being represented by formula (IV-b), in the presence of POCl₃.



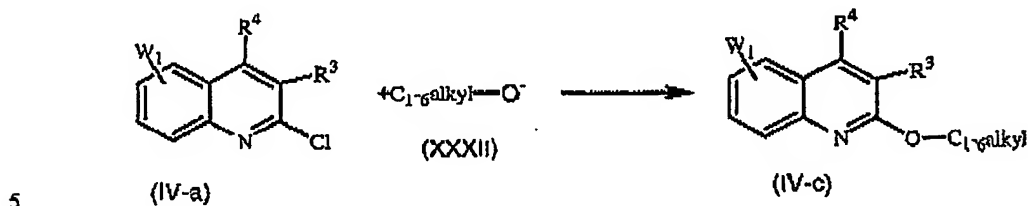
Intermediates of formula (IV-a), wherein R⁴ is hydrogen, said intermediates being represented by formula (IV-a-1), can also be prepared by reacting an intermediate of formula (XXIX) with POCl₃ in the presence of *N,N*-dimethylformamide (Vilsmeier-Haack formylation followed by cyclization).



Intermediates of formula (XXIX) may be prepared by reacting an intermediate of formula (XXX) with an intermediate of formula (XXXI), wherein W₁ represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as for example *N,N*-diethylethanamine, and a suitable reaction-inert solvent, such as methylene chloride.



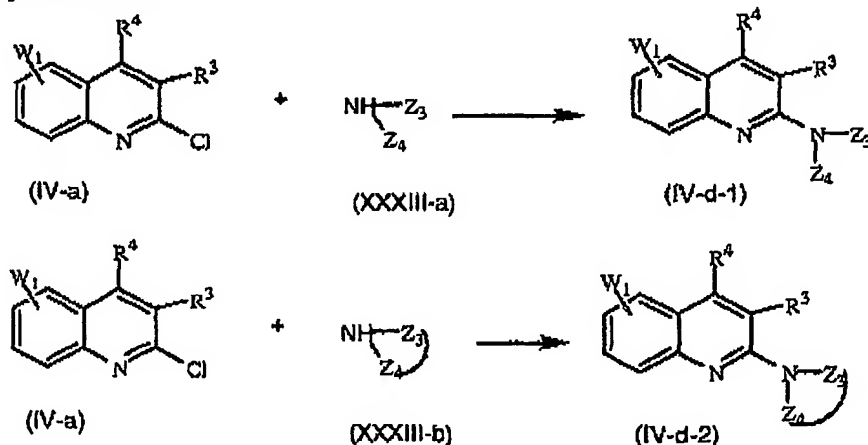
Intermediates of formula (IV-a) can be converted into an intermediate of formula (IV-c) by reaction with an intermediate of formula (XXXII) in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.



Intermediates of formula (IV-a) can also be converted into an intermediate of formula (IV-d-1) by reaction with a suitable amine of formula (XXXIII-a), wherein Z₃ and Z₄ each independently represent hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl or into an intermediate of formula (IV-d-2) by reaction with a suitable amine of formula (XXXIII-b), wherein Z₃ and Z₄ are taken together to form a heterocycle as defined hereinabove in the definition of R² provided that the heterocycle comprises at least one nitrogen atom, in the presence of a suitable base, such as for example dipotassium carbonate, and a reaction-inert solvent, such as *N,N*-dimethylformamide.

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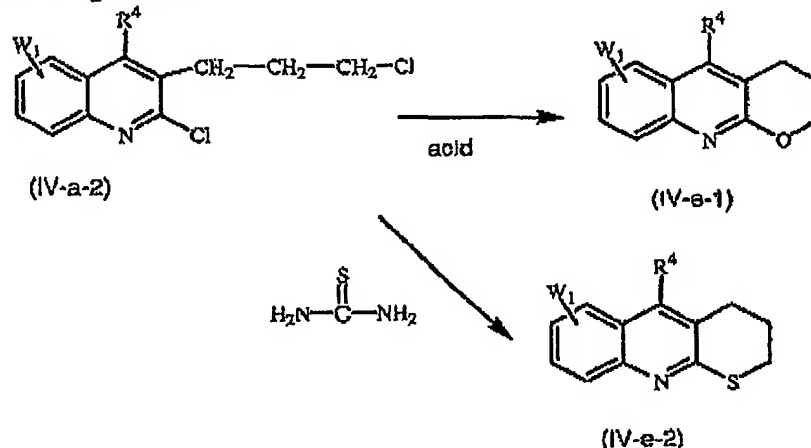


Intermediates of formula (IV-a), wherein R³ represents CH₂-CH₂-CH₂-Cl, said intermediates being represented by formula (IV-a-2), can also be converted into an intermediate of formula (IV), wherein R² and R³ are taken together to form a bivalent radical of formula -O-CH₂-CH₂-CH₂-, said intermediate being represented by formula (IV-e-1), by reaction with a suitable acid, such as hydrochloric acid and the like.

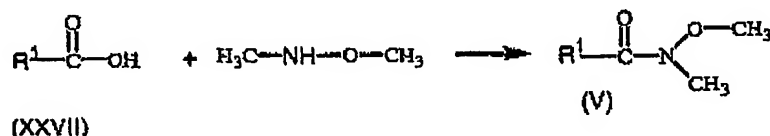
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Intermediates of formula (IV-a-2) can also be converted into an intermediate of formula (IV), wherein R² and R³ are taken together to form a bivalent radical of formula

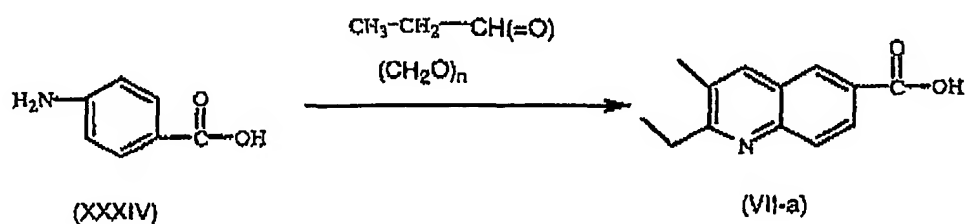
-S-CH₂-CH₂-CH₂-, said intermediate being represented by formula (IV-e-2), by reaction with H₂N-C(=S)-NH₂ in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. ethanol.



- 5 Intermediates of formula (V) may be prepared by reacting an intermediate of formula (XXVII) with an intermediate of formula CH₃-NH-O-CH₃ in the presence of 1,1'-carbonyldiimidazole and a suitable reaction-inert solvent, such as methylene chloride.

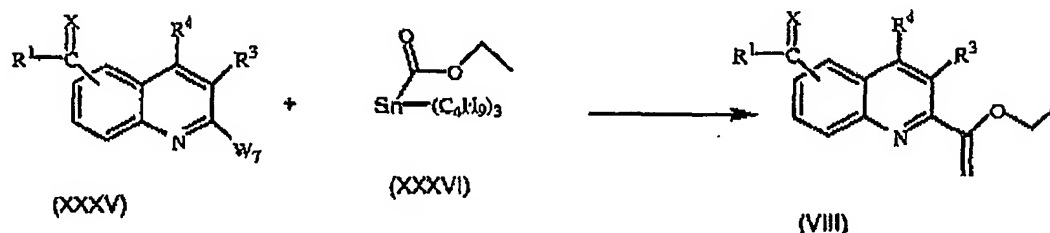


- 10 Intermediates of formula (VII), wherein Q represents a quinoline moiety, in particular a quinoline moiety wherein R² is ethyl, R³ is methyl and R⁴ is hydrogen, and the carboxyl moiety is placed in position 6, said intermediates being represented by formula (VII-a), can be prepared by reaction an intermediate of formula (XXXIV) in the presence of a suitable aldehyde, such as CH₃-CH₂-CH(=O), (CH₂O)_n, ZnCl₂, FeCl₃ and a suitable reaction-inert solvent, such as an alcohol, for example ethanol.



- Intermediates of formula (VIII) can be prepared by reacting an intermediate of formula (XXXV) with an intermediate of formula (XXXVI) in the presence of a suitable
- 20

catalyst, such as for example tetrakis(triphenylphosphine)palladium and a suitable reaction-inert solvent, such as for example dioxane.



Still some other preparations can be devised, some of them are disclosed further in this application with the Examples.

- 10 Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g. liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by the selective crystallization of their
- 15 diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. Preferably, if a specific stereoisomer is desired, said
- 20 compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chirally pure starting materials. Stereoisomeric forms of the compounds of formula (I) are obviously intended to be included within the scope of the invention.
- 25 A stereoisomer of a compound of formula (I-A) or (I-B) such as a *cis* form, may be converted into another stereoisomer such as the corresponding *trans* form by reacting the compound with a suitable acid, such as hydrochloric acid, in the presence of a suitable reaction-inert solvent, such as for example tetrahydrofuran.
- 30 The mGluR1 antagonistic activity of the present compounds can be demonstrated in the Signal transduction on cloned rat mGluR1 in CHO cells test and the Cold allodynia test in rats with a Bennett ligation, as described hereinafter.

Due to their mGluR antagonistic activity, more in particular their Group I mGluR antagonistic activity and even more in particular, their mGluR1 antagonistic activity, the compounds of formula (I-A) or (I-B), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms are useful in the treatment or prevention of glutamate-induced diseases of the central nervous system. Diseases in which a role for glutamate has been demonstrated include drug addiction or abstinence (dependence, opioid tolerance, opioid withdrawal), hypoxic, anoxic and ischemic injuries (ischemic stroke, cardiac arrest), pain (neuropathic pain, inflammatory pain, hyperalgesia), hypoglycemia, diseases related to neuronal damage, brain trauma, head trauma, spinal cord injury, myelopathy, dementia, anxiety, schizophrenia, depression, impaired cognition, amnesia, bipolar disorders, conduct disorders, Alzheimer's disease, vascular dementia, mixed (Alzheimer's and vascular) dementia, Lewy Body disease, delirium or confusion, Parkinson's disease, Huntington's disease, Down syndrome, epilepsy, aging, Amyotrophic Lateral Sclerosis, multiple sclerosis, AIDS (Acquired Immune Deficiency Syndrome) and AIDS related complex (ARC).

The present invention also provides compositions for the administration to mammals, in particular humans, in particular for diagnostic reasons, more in particular for imaging an organ comprising a therapeutically effective amount of a radiolabelled compound of formula (I-A)* or (I-B)* and a pharmaceutically acceptable carrier or diluent.

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, a therapeutically effective amount of a particular compound, in base or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, topically, percutaneously or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, emulsions, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills,

capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs e.g. creams, gel, dressings, shampoos, tinctures, pastes, ointments, salves, powders and the like. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The diagnostically effective dose or frequency of administration depends on the particular compound of formula (I-A)* or (I-B)* used and the particular condition of the mammal being treated, as is well known to those skilled in the art.

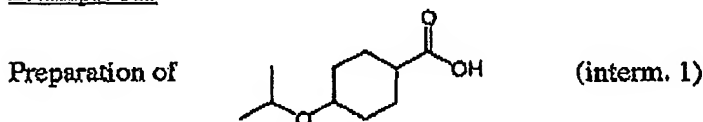
The following examples are intended to illustrate and not to limit the scope of the present invention.

Experimental part

- Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropylether, "DMSO" is defined as dimethylsulfoxide, "BHT" is defined as 2,6-bis(1,1-dimethylethyl)-4-methylphenol, and "THF" is defined as tetrahydrofuran.

A. Preparation of the intermediates

Example A1

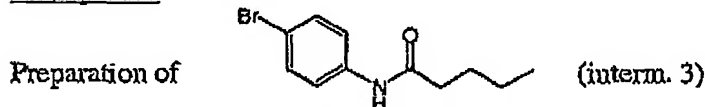


- 10 A mixture of 4-(1-methylethoxy)benzoic acid (0.083 mol) and Rh/Al₂O₃ 5% (10g) in THF (220ml) was hydrogenated at 50°C (under 3 bar pressure of H₂) for 1 night. The mixture was filtered over celite, washed with THF and evaporated. Yield: 16g of intermediate 1 (100%).

Example A2

- 15 Preparation of 2-ethyl-3-methyl-6-quinolinecarboxylic acid (interm. 2)
A mixture of 4-aminobenzoic acid (0.299 mol) in ethanol (250ml) was stirred at room temperature. ZnCl₂ (0.0367 mol) and (CH₂O)_n (10g) were added. FeCl₃·6H₂O (0.5 mol) was added portionwise and the temperature rised till 60-65°C. Propanal (30ml) was added dropwise over a 2 hours period. The mixture was refluxed for 2 hours and
20 kept at room temperature for 12 hours. The mixture was poured into water and filtered through celite. The filtrate was acidified till pH=7 with HCl 6N and the mixture was evaporated till dryness. The residue was used without further purification. Yield : 56.1g of 2-ethyl-3-methyl-6-quinolinecarboxylic acid (interm. 2).

Example A3



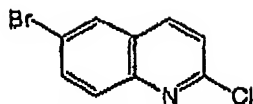
- 25 Pentanoyl chloride (0.2784 mol) was added at 5°C to a mixture of 4-bromobenzenamine (0.232 mol) and *N,N*-diethylethanamine (0.2784 mol) in CH₂Cl₂ (400ml). The mixture was stirred at room temperature overnight, poured out into water and extracted with CH₂Cl₂. The organic layer was separated, washed with a concentrated NH₄OH solution and water, dried (MgSO₄), filtered and the solvent was
30 evaporated. The residue (60g) was crystallized from diethylether. The precipitate was

filtered off and dried. The residue (35g, 63%) was taken up in CH_2Cl_2 . The organic layer was separated, washed with a 10% K_2CO_3 solution, washed with water, dried (MgSO_4), filtered and the solvent was evaporated. Yield: 30g of intermediate (3) (54%).

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Example A4

Preparation of

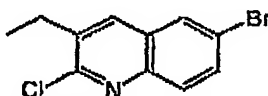


(interm. 4)

A mixture of 6-bromo-2(1H)-quinolinone (0.089 mol) in POCl₃ (55ml) was stirred at 60°C overnight, then at 100°C for 3 hours and the solvent was evaporated. The residue was taken up in CH₂Cl₂, poured out into ice water, basified with NH₄OH conc., filtered
5 over celite and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 14.5g of intermediate (4) (67%).

Example A5

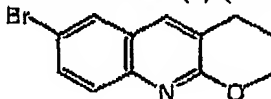
a) Preparation of



(interm. 5)

DMF (37ml) was added dropwise at 10°C under N₂ flow to POCl₃ (108ml). After
10 complete addition, the mixture was allowed to warm to room temperature. N-(4-bromophenyl)butanamide (0.33 mol) was added portionwise. The mixture was stirred at 85°C overnight, then allowed to cool to room temperature and poured out on ice (exothermic reaction). The precipitate was filtered off, washed with a small amount of water and dried (vacuum). The residue was washed with EtOAc/diethyl ether and
15 dried. Yield: 44.2g of intermediate (5) (50%).

b) Preparation of

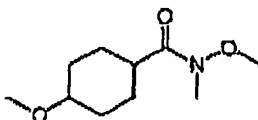


(interm. 6)

A mixture of intermediate (5) (0.162 mol) in methanol (600ml), and a solution of methanol sodium salt in methanol at 35% (154ml) was stirred and refluxed overnight. The mixture was poured out on ice. The precipitate was filtered off, washed with a small amount of water and taken up in CH₂Cl₂. K₂CO₃ 10% was added and the mixture
20 was extracted with CH₂Cl₂. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 31.9g of intermediate (6) (74%).

Example A6

Preparation of



(interm. 7)

1,1'-Carbonylbis-1H-imidazole (0.074 mol) was added portionwise to a mixture of
25 4-methoxycyclohexanecarboxylic acid (0.063 mol) in CH₂Cl₂ (200ml). The mixture

was stirred at room temperature for 1 hour. Then *N*-methoxymethanamine (0.074 mol) was added. The mixture was stirred at room temperature overnight, poured out into H₂O and extracted with CH₂Cl₂. The organic layer was separated, washed several times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 12.6g of interm. 7.

Example A7

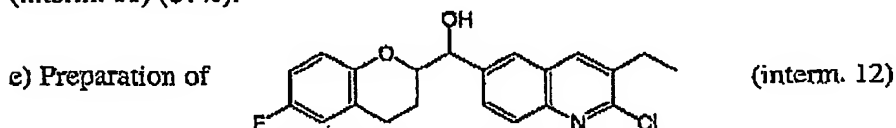
a) A mixture of 6-fluoro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid (0.30mol) in acetic acid (400ml) was hydrogenated with Pd/C (3g) as a catalyst. After uptake of H₂ (3 equiv), the catalyst was filtered off. The filtrate was evaporated. The residue was stirred in petroleum ether. The precipitate was filtered off and dried (vacuum; 70°C). After recrystallization from CHCl₃/CH₃OH, the precipitate was filtered off and dried (vacuum; 80°C and high vacuum; 85°C). Yield: 8.8 g of 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid (interm. 8) (15.0%).

b) A mixture of intermediate (8) (0.255 mol) in ethanol (400ml) and H₂SO₄ (5ml) was stirred and refluxed for 8 hours. The solvent was evaporated till dryness. The residue was dissolved in CH₂Cl₂. The organic layer was separated, washed with K₂CO₃ 10%, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 45g of ethyl 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-carboxylate (interm. 9) (79%).

c) Reaction under N₂. A mixture of sodium bis(2-methoxyethoxy)aluminumhydride, 70 wt % solution in methylbenzene 3.4M (0.44 mol) in benzene (150 ml) (reflux) was added dropwise during 1 hour to a refluxed mixture of interm. 9 (0.22 mol) and benzene (600 ml). After stirring for 2.5 hours at reflux temperature, the mixture was cooled to ±15°C. The mixture was decomposed by adding dropwise ethanol (30 ml) and water (10 ml). This mixture was poured out onto ice/water and this mixture was acidified with concentrated hydrochloric acid. This mixture was extracted with diethyl ether (500 ml). The separated organic layer was washed with water, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CHCl₃). The desired fraction was collected and the eluent was evaporated. Yield: 34 g of 6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol (interm. 10) (85%).

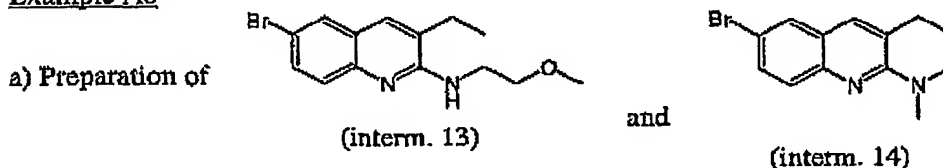
d) Reaction under N₂. To a stirred and cooled (-60°C; 2-propanone/CO₂ bath) mixture of ethanedioyl dichloride (0.1 mol) in CH₂Cl₂ (350 ml) was added sulfinylbis[methane] (30 ml) during 10 minutes. After stirring 10 minutes, a mixture of interm. 10 in CH₂Cl₂ (90 ml) was added during 5 minutes. After stirring for 15 minutes, *N,N*-diethylethanamine (125 ml) was added. When the mixture was warmed up to room temperature, it was poured out in water. The product was extracted with CH₂Cl₂.

The organic layer was washed with water, HCl (1M), water, NaHCO₃ (10%) and water, dried and evaporated. The residue was dissolved in diethyl ether, washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel (eluent : CHCl₃). The desired fraction was collected and the eluent was evaporated. Yield: 21.6 g of 6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde (interm. 11) (67%).

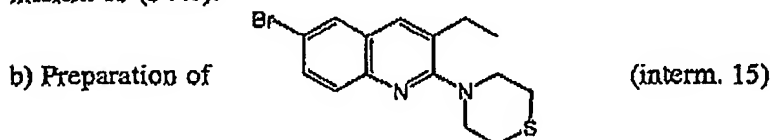


nButyllithium 1.6M (0.056 mol) was added slowly at -70°C to a solution of intermediate (5) (0.046 mol) in THF (100ml). The mixture was stirred at -70°C for 30 minutes. A suspension of interm. 11 (0.056 mol) in THF (100ml) was added slowly. The mixture was stirred at -70°C for 1 hour, then brought to room temperature, poured out into H₂O and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (21g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/10; 15-35µm). The pure fractions were collected and the solvent was evaporated. Yield: 9.5g of interm. 12 (55%).

Example A8



A mixture of intermediate (5) (0.1127 mol), 2-methoxyethanamine (0.2254 mol) and K₂CO₃ (0.2254 mol) in DMF (500ml) was stirred at 120°C for 15 hours and then cooled. The solvent was evaporated. The residue was taken up in CH₂Cl₂ and H₂O. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated till dryness. The residue (33.53g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.5/0.5; 15-40 µm). Two fractions were collected and their solvents were evaporated. Yield: 5.7g of interm. 14 (38%) and interm. 13 (34%).



A mixture of intermediate (5) (0.0751 mol), thiomorpholine (0.0891 mol) and K₂CO₃ (0.15 mol) in DMF (200ml) was stirred at 120°C for 12 hours. The solvent was

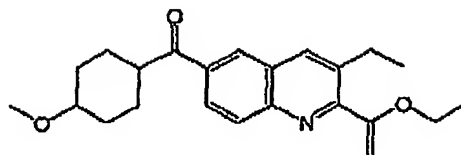
evaporated till dryness. The residue was taken up in CH_2Cl_2 and H_2O . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (26g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 20-45 μm). Two fractions were collected and their solvents were evaporated. The two fractions were combined. Yield: 9.4g of interm. 15 (37%); mp. 82°C.

Example A9

- a) 4-Aminobenzoic acid (0.219 mol) was added to a solution of sodium 3-nitrobenzenesulfonate (0.118 mol) in H_2SO_4 70% (230ml) and the mixture was stirred and refluxed. 2-propene-1,1-diol, 2-methyl-, diacetate (0.216 mol) was added dropwise and the mixture was refluxed for 4 hours. Ethanol (200ml) was added and the mixture was stirred at 80°C for 48 hours. The mixture was evaporated, the residue was poured into ice water/ NH_4OH and extracted with CH_2Cl_2 . The organic layer was dried (MgSO_4) and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2 /2-propanol 99/1). The pure fractions were collected and evaporated. Yield : 21g of ethyl 3-methyl-6-quinolinecarboxylate (interm. 16) (45%).
- b) Interm. 16 (0.098 mol) in THF (270ml) was added at 0°C to a solution of LiAlH_4 (0.098 mol) in THF under N_2 . When the addition was complete, water (10ml) was added. The precipitate was filtered off and washed with CH_2Cl_2 . The organic layer was dried (MgSO_4), filtered off and evaporated. The product was used without further purification. Yield : 16.71g of 3-methyl-6-quinolinemethanol (interm. 17).
- c) MnO_2 (0.237 mol) was added to a solution of interm. 17 (0.096 mol) in CH_2Cl_2 (200ml) and the mixture was stirred at room temperature for 12 hours. The mixture was filtered through celite and the filtrate was stirred again with MnO_2 (20g) for 12 hours. MnO_2 (10g) was added again. The mixture was stirred for 12 hours. The mixture was filtered through celite and evaporated. The product was used without further purification. Yield : 11.71g of 3-methyl-6-quinolinecarboxaldehyde (71%) (interm. 18).
- d) A solution of bromocyclohexyl (0.14 mol) in 1,1'-oxybisethane (50ml) and Mg turnings (50ml) was added at 10°C to a mixture of THF (0.14 mol) in 1,1'-oxybisethane (10ml). A solution of interm. 18 (0.07 mol) in Mg turnings (100ml) was added carefully at 5°C, the mixture was poured into ice water and extracted with EtOAc. Yield : 11.34g of (\pm)- α -cyclohexyl-3-methyl-6-quinolinemethanol (63%) (interm. 19).

Example A10

Preparation of

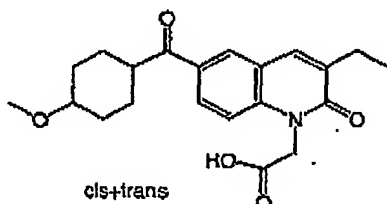


(interm. 20)

A mixture of compound (5) (0.001507 mol), tributyl(1-ethoxyethenyl)stannane (0.00226 mol) and $\text{Pd}(\text{PPh}_3)_4$ (0.000151 mol) in 1,4-dioxane (5ml) was stirred at 80°C for 3 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. This product was used without further purification. Yield: 1.4g of interm. 20.

Example A11

Preparation of

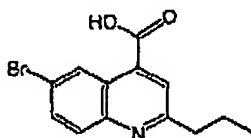


(interm. 21)

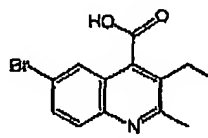
A mixture of compound (45) (prepared according to B6) (0.00125 mol) in NaOH 3N (5 ml) and iPrOH (1.7 ml) was stirred at room temperature overnight, then poured out into H_2O , acidified with HCl 3N and extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was taken up in diethyl ether. The precipitate was filtered off and dried. Yielding: 0.26 g of intermediate 23 (56%). (mp.: 232°C)

Example A12

a. Preparation of



(interm. 22)

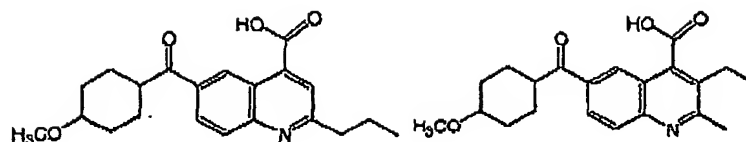


(interm. 23)

A mixture of 5-bromo-1H-indole-2,3-dione (0.221 mol) in NaOH 3N (500 ml) was stirred at 80°C for 30 minutes, brought to room temperature and 2-pentanone (0.221 mol) was added. The mixture was stirred and refluxed for 1 hour and 30 minutes and acidified with AcOH until pH=5. The precipitate was filtered, washed with water and dried. Yielding 52.3 g of intermediate 24 and intermediate 25. (Total yielding: 80%).

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b. Preparation of



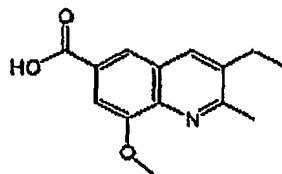
(interm. 24)

(interm. 25)

nBuLi 1.6 M (0.0816 mol) was added dropwise at -78°C to a suspension of intermediate 25 (0.034 mol) and intermediate 26 (0.034 mol) in THF (300 ml) under N_2 flow. The mixture was stirred at -78°C for 30 minutes. nBuLi 1.6M (0.0816 mol) was added dropwise. The mixture was stirred for 1 hour. A mixture of intermediate 9 (0.102 mol) in THF (250 ml) was added slowly. The mixture was stirred for -78°C to -20°C , poured out into $\text{H}_2\text{O}/\text{HCl}$ 3N and extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated till dryness. Yielding: 20.89 g of compound intermediate 26 and intermediate 27 (86%).

Example A13

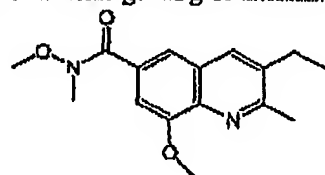
a. Preparation of



(interm. 26)

4-amino-3-methoxybenzoic acid (0.054 mol) was added portionwise at room temperature to a solution of 3-chloro-2-ethyl-2-butenal (0.065 mol) in AcOH (100ml). The mixture was stirred and refluxed for 8 hours and evaporated to dryness. The residue was taken up in CH_2Cl_2 , water was added and the solution was basified by Et_3N . The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: 2.5g of interm. 26 (18%).

b. Preparation of



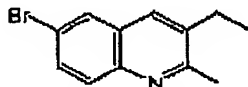
(interm. 27)

CDI (0.012 mol) was added at room temperature to a solution of interm. 26 (0.011 mol) in CH_2Cl_2 (30ml). The mixture was stirred at room temperature for 1 hour. methoxyaminomethyl (0.012 mol) was added and the mixture was stirred at room temperature for 8 hours. H_2O was added. A precipitate was filtered off. The filtrate was extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered, and

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the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.95g of interm. 27 (31%) (mp.: 148°C).

Example A14



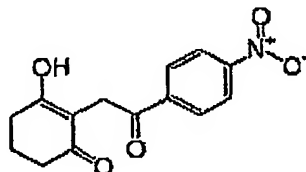
Preparation of

(interm. 28)

- 5 4-Bromobenzenamine (0.034 mol) was added at room temperature to a solution of 3-chloride-2-ethyl-2-butanal (0.041 mol) in AcOH (60 ml). The mixture was stirred and refluxed for 8 hours, brought to room temperature and evaporated to dryness. The product was crystallized from EtOAc. The precipitate was filtered, washed with K₂CO₃ 10% and taken up in CH₂Cl₂. The organic layer was separated, dried
- 10 (MgSO₄), filtered, and the solvent was evaporated. Yielding: 4,6 g of interm. 28 (54%).

Example A15

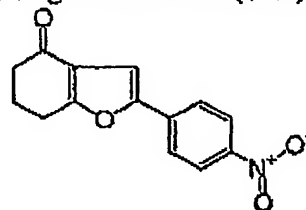
a. Preparation of



(interm. 29)

- A solution of KOH (0.326 mol) in H₂O (150ml) was added slowly at 5°C to a solution of 1,3-cyclohexanedione (0.268 mol) in H₂O (150ml). The temperature must not reach
- 15 12 °C. KI (2g) then 2-bromo-1-(4-nitrophenyl)ethanone (0.294 mol) were added portionwise. The mixture was stirred at room temperature for 48 hours. The precipitate was filtered, washed with H₂O then with diethyl ether and dried. Yielding: 63g (85%). A part of this fraction (1g) was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 0.5g of interm. 29 (42%) (mp.: 100°C).

b. Preparation of

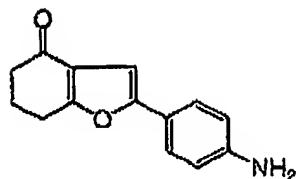


(interm. 30)

- 20 A mixture of interm. 29 (0.145 mol) in H₂SO₄ (40ml) was stirred at room temperature for 1 hour, poured out into ice, basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 31g (58%). A part of this fraction (1g) was crystallized from EtOH. The
- 25 precipitate was filtered off and dried. Yielding: 0.7g of interm. 30 (58%) (mp.: 200°C).

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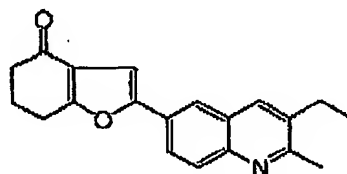
c. Preparation of



(interm. 31)

A mixture of interm. 30 (0.039 mol), Raney Ni (10g) in EtOH (100ml) was hydrogenated at room temperature under a 3 bar pressure for 1 hour. The mixture was filtered over celite and washed with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. The residue (9.5g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 4.6g (52%). The filtrate was evaporated. The residue (2.7g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$; 99/1; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yielding: 1.6g F1 and 1.2g F2. F2 was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 0.24g of interm. 31 (2%) (mp.: 202°C).

d. Preparation of

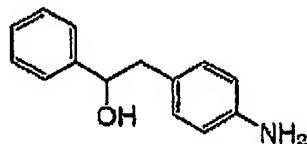


(interm. 32)

Interm. 30 (0.02 mol) was added at room temperature to a solution of 3-chloro-2-ethyl-2-butenal (0.04 mol) in AcOH (50ml). The mixture was stirred and refluxed for 4 hours. The solvent was evaporated till dryness. The residue was crystallized from EtOAc. The precipitate was filtered off and dried. The residue was taken up in CH_2Cl_2 . The mixture was basified with K_2CO_3 10% and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered, and the solvent was evaporated. The residue was crystallized from EtOH. The precipitate was filtered off and dried. Yielding: 2.5g of interm. 32 (40%).

Example A16

Preparation of



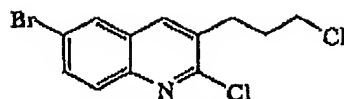
(interm. 33)

A mixture of 2-(4-nitrophenyl)-1-phenylethanone (0.083 mol) and Raney Ni (20g) in EtOH (200ml) was hydrogenated at room temperature for 1 hour under a 3 bar pressure, then filtered over celite, washed with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ and dried. Yielding: 17.5g of interm. 33 (97%).

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Example A17

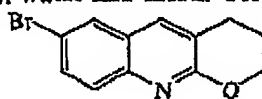
a. Preparation of



(interm. 34)

DMF (12.4ml) was added dropwise at 5°C to POCl₃ (0.7536 mol). 4'-bromo-5-chloro-1-(3-chloropropyl)quinoline (0.1032 mol) was added and the mixture was stirred at 75°C for 6 hours, cooled at room temperature and poured out into ice water. The insoluble was filtered, washed with water and dried. Yielding: 25.7g of intermediate 34 (78%).

b. Preparation of

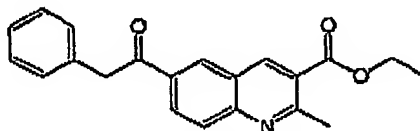


(interm. 35)

A mixture of intermediate 34 (0.094 mol) in HCl 6N (250ml) was stirred and refluxed for 2 days, cooled, poured out on water (100ml) and neutralized with NH₄OH (concentrated). The insoluble was filtered and washed with water then with EtOH. Yielding: 19g. The filtrate was evaporated. The residue (9.4g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99.25/0.75; 15-35μm). One fraction was collected and the solvent was evaporated. Yielding: 8g of intermediate 35 (32%).

15 B. Preparation of the non-radioactive compoundsExample B1

Preparation of



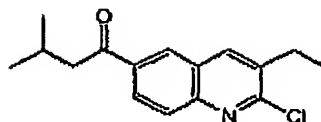
(compound 306)

POCl₃ (0.024 mol) was added slowly at 5°C to DMF (0.024 mol). The mixture was stirred at room temperature for 30 minutes, then cooled to 5°C. 3-Oxo-butanoic acid ethyl ester (0.024 mol) was added slowly. The mixture was stirred at 5°C for 30 minutes. 1-(4-aminophenyl)-2-phenylethanone (0.024 mol) was added portionwise. The mixture was stirred at 90°C for 3 hours and dissolved in CH₂Cl₂. Ice water was added. The mixture was basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.9 g of compound 306 (11%) (mp.:136°C).

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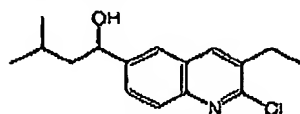
Example B2

Preparation of



(compound 2)

KMnO₄ (10g) was added portionwise at room temperature to a solution of

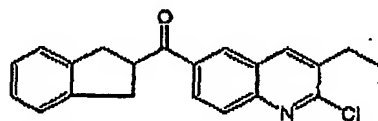


(prepared according to example A7.e) (0.022 mol)

in tris(dioxa-3,6-heptyl)amine (1ml) and CH₂Cl₂ (100ml). The mixture was stirred at room temperature for 8 hours, filtered over celite, washed with CH₂Cl₂ and dried. The residue (6g, 100%) was crystallized from diethyl ether/petroleum ether. The precipitate was filtered off and dried. Yield: 2g of compound (2) (33%); mp. 82°C.

Example B3

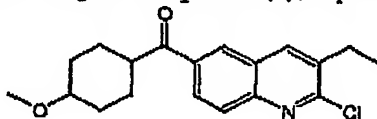
a) Preparation of



(compound 3)

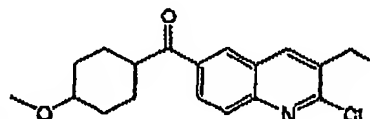
nBuLi 1.6M (0.07 mol) was added slowly at -70°C to a solution of intermediate (5) (0.058 mol) in THF (150ml). The mixture was stirred at -70°C for 30 minutes. A solution of 2,3-dihydro-1H-Indene-2-carbonitrile (0.07 mol) in THF (100ml) was added slowly. The mixture was stirred at -70°C for 1 hour, brought slowly to room temperature, hydrolyzed with H₂O and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (22g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 80/20 to 100; 15-35µm). The pure fractions were collected and the solvent was evaporated. The second fraction was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yield: 0.11g of compound (3). The filtrate was concentrated. Yield: 0.55g of compound (3); mp. 145°C.

b) Preparation of



cis (compound 4)

and



trans (compound 5)

nBuLi 1.6M (0.022 mol) was added slowly at -70°C to a solution of intermediate (5) (0.018 mol) in THF (50ml). The mixture was stirred at -70°C for 1 hour, brought to -40°C, then cooled to -70°C. A solution of interm. 7 (0.018 mol) in THF (40ml) was added slowly. The mixture was stirred at -70°C for 1 hour, then brought to -20°C, hydrolyzed with H₂O and extracted with EtOAc. The organic layer was separated,

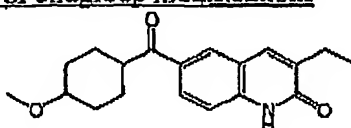
A solution of chloromethylbenzene (0.0069 mol) in diethyl ether (8ml) was added slowly to a suspension of Mg (0.0069 mol) in a small amount of diethyl ether. The mixture was stirred at room temperature for 30 minutes (disappearance of Mg), then cooled to 5°C. A solution of int. 27 (0.0027 mol) in THF (8ml) was added slowly. The mixture was stirred at 5°C for 15 minutes, then at room temperature for 2 hours, poured out into H₂O and filtered over celite. The precipitate was washed with EtOAc. The filtrate was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (1g) was purified by column chromatography over kromasil (eluent: CH₂Cl₂ 100 to CH₂Cl₂/CH₃OH 99/1; 15-40µm). The pure fractions were collected and the solvent was evaporated. The

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residue (0.5g, 56%) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.14g of compound 503 (15%).

Example B4: examples of endgroup modifications

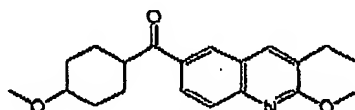
a) Preparation of



(compound 156)

trans

A mixture of

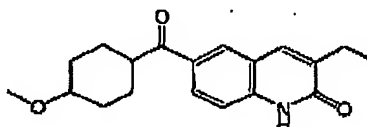


(compound 8)

trans

- 5 (prepared according to example B3.c) (0.018 mol) in HCl 3N (60ml) and THF (60ml) was stirred at 60°C overnight. The mixture was basified with a K₂CO₃ 10% solution and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 4.6g of compound (156) (82%).

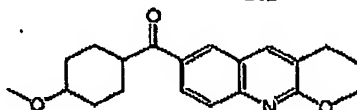
b) Preparation of



(compound 9)

cis

A mixture of

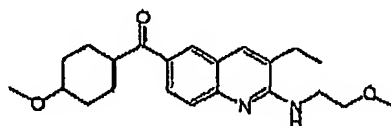


(compound 7)

cis

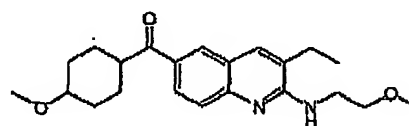
- 10 (prepared according to example B3.c) (0.0122 mol) in HCl 3N (40ml) and THF (40ml) was stirred and refluxed overnight, poured out into water, basified with K₂CO₃ 10% and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 40/60; 15-40μm). The pure fractions were
15 collected and the solvent was evaporated. Yield: 2g of compound (9) (52%); mp. 226°C.

c) Preparation of



cis (compound 10)

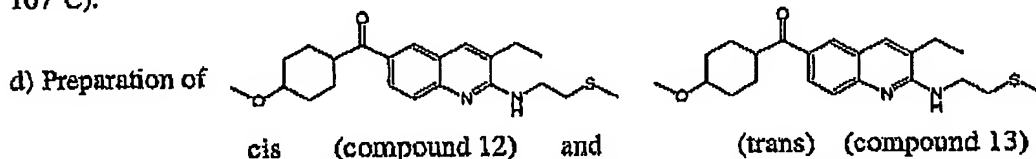
and



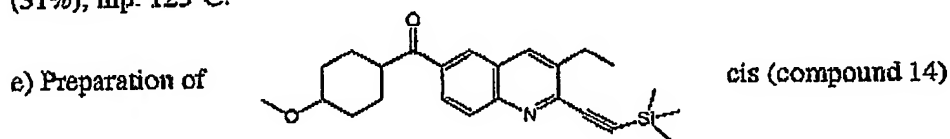
(trans) (compound 11)

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A mixture of compound (4) (0.0015 mol), 2-methoxyethanamine (0.003 mol) and K_2CO_3 (0.003 mol) in DMF (5ml) was stirred at 140°C for 48 hours. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40; 15-40 μ m). Two fractions were collected and the solvent was evaporated. Both fractions were crystallized separately from pentane. The precipitate was filtered off and dried. Yield: 0.05g of compound (10) (9%; mp. 115°C) and 0.057g of compound (11) (10%; mp. 107°C).



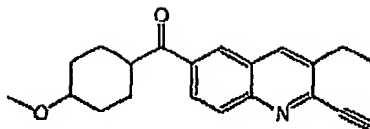
A mixture of compound (4) (0.0015 mol) in 2-(methylthio)ethanamine (2ml) was stirred at 120°C for 8 hours. K_2CO_3 10% was added. The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40 μ m). Two fractions were collected and the solvent was evaporated. The first fraction was crystallized from diethyl ether/petroleum ether. The precipitate was filtered off and dried. Yield: 0.08g of compound (12) (14%); mp. 120°C. The second fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.18g of compound (13) (31%); mp. 125°C.



A mixture of compound (4) (0.001507 mol), ethynyltrimethylsilane (0.003013 mol), CuI (0.000151 mol) and $Pd(PPh_3)_4$ (0.000151 mol) in *N,N*-diethylethanamine (5ml) was stirred at 100°C for 24 hours. Water was added. The mixture was filtered over celite, washed with EtOAc and the filtrate was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (1.3g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue (0.3g) was crystallized from pentane. The precipitate was filtered off and dried. Yield: 0.11g of compound (14) (18%); mp. 114°C.

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f) Preparation of

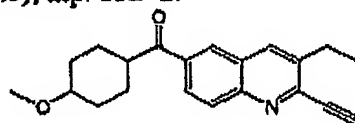


(compound 15)

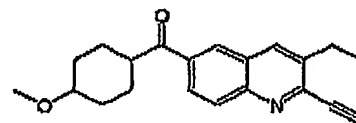
cis

A mixture of compound (14) (0.013 mol) and KF (0.038 mol) in acetic acid (50ml) was stirred at room temperature for 2 hours. H₂O was added and the mixture was extracted with diethyl ether. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (4.4g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40μm). One fraction was collected and the solvent was evaporated. This fraction (3g, 73%) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 2.45g of compound (15) (60%); mp. 132°C.

g) Preparation of

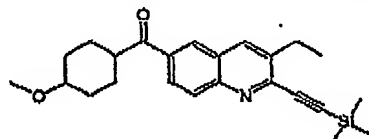


cis (compound 15) and

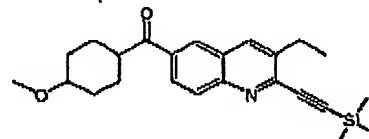


trans (compound 17)

A mixture of



cis (compound 14) and



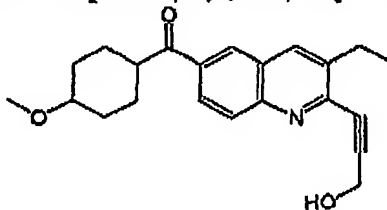
trans (compound 16)

prepared according to example B.7.a) (0.0056 mol) in KOH [1M, H₂O] (10ml) and methanol (30ml) was stirred at room temperature for 1 hour, poured out into water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15 to 70/30; 15-40μm). Two fractions were collected and the solvent was evaporated.

The first fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.2g of compound (15) (11%); mp. 133°C.

The second fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.3g of compound (17) (16%); mp. 128°C.

h) Preparation of



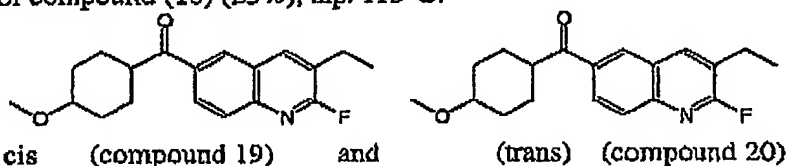
(compound 18)

- 50 -

cis

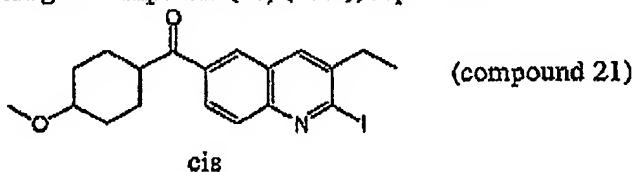
- A mixture of compound (4) (0.001205 mol), 2-propyn-1-ol (0.002411 mol), $\text{Pd}(\text{PPh}_3)_4$ (0.000121 mol) and CuI (0.000121 mol) in *N,N*-diethylethanamine (5ml) was stirred at 100°C for 2 hours. Water was added. The mixture was filtered over celite, washed with EtOAc and extracted with EtOAc . The organic layer was separated, dried
- 5 (MgSO₄), filtered and the solvent was evaporated. The residue (0.7g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15–40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from petroleum ether and diethyl ether. The precipitate was filtered off and dried. Yield: 0.1g of compound (18) (23%); mp. 113°C .

i) Preparation of



- 10 A mixture of compound (4) (0.006027 mol) and KF (0.024108 mol) in DMSO (20ml) was stirred at 140°C . The solvent was evaporated till dryness. The residue was solidified in water and diethyl ether. The mixture was extracted with diethyl ether. The organic layer was separated, washed with diethyl ether, washed with a saturated solution of NaCl , dried (MgSO₄), filtered and the solvent was evaporated. The residue
- 15 (1.7g) was purified by column chromatography over silica gel (eluent: cyclohexane/ EtOAc 85/15; 15–40 μm). Three fractions were collected and their solvents were evaporated.
- The first fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.21g of compound (19) (11%); mp. 92°C .
- 20 The second fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.33g of compound (20) (17%); mp. 114°C .

j) Preparation of

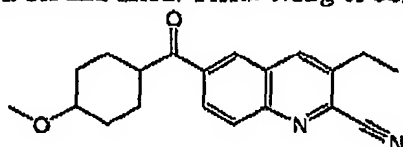


- A mixture of compound (4) (0.003013 mol), acetyl chloride (0.003315 mol) and sodium iodide (0.006027 mol) in CH_3CN (10ml) was stirred and refluxed for 1 hour. K_2CO_3 10% was added. The mixture was extracted with CH_2Cl_2 . The organic layer
- 25 was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1g) was purified by column chromatography over silica gel (eluent: cyclohexane/ EtOAc 80/20; 15–40 μm). Two fractions were collected and their solvents

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were evaporated. The first fraction was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.12g of compound (21); mp. 110°C.

k) Preparation of

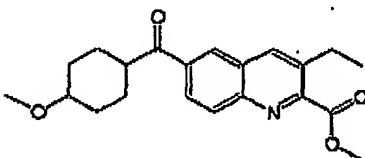


(compound 22)

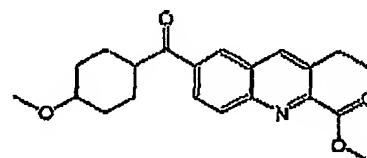
cis

A mixture of compound (21) (0.000898 mol), trimethylsilanecarbonitrile (0.001347 mol) and $\text{Pd(PPh}_3)_4$ (0.00009 mol) in *N,N*-diethylethanamine (5ml) was stirred at 100°C for 2 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (0.4g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.18g, 62%) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield : 0.13g of compound (22) (45%); mp. 138°C.

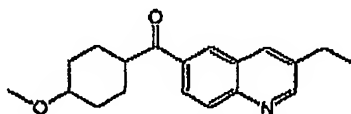
l) Preparation of



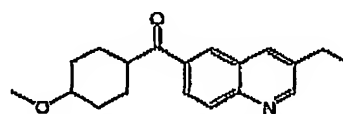
cis (compound 23)



(trans) (compound 24)



cis (compound 25)



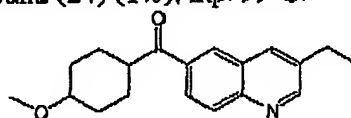
(trans) (compound 26)

A mixture of compound (4) (0.00603 mol), Pd(OAc)_2 (0.000603 mol), PPh_3 (0.00904 mol) and K_2CO_3 (0.012054 mol) in CO (gas) and methanol (40ml) was stirred at 90°C for 8 hours under a 5 bar pressure of CO. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 100/0 to 98/2; 15-35 μm). Four fractions (F1-F4) were collected and the solvent was evaporated. Yield: 0.13g (cis) F1; 0.02g F2 (cis, compound 25); 0.055g F3 (trans, 3%) and 0.11g F4 (trans; compound 26). F1 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.03g of compound (23) (1%); mp. 91°C.

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F3 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.035g of compound (24) (1%); mp. 99°C.

m) Preparation of

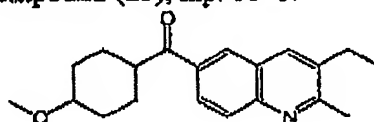


(compound 25)

cis

A mixture of compound (4) (0.009 mol) and Zn (0.027 mol) in acetic acid (30ml) was stirred at 60°C for 4 hours, filtered over celite, washed with CH₂Cl₂, evaporated till dryness, solubilized in CH₂Cl₂ and washed with K₂CO₃ 10%. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (4g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 75/25; 15-40µm). One fraction was collected and the solvent was evaporated. This fraction (1g 37%) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: compound (25); mp. 88°C.

n) Preparation of

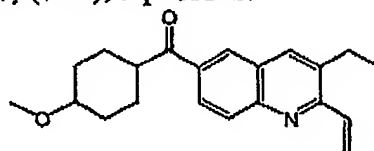


(compound 27)

cis

A mixture of compound (4) (0.001502 mol), Sn(CH₃)₄ (0.003004 mol) and Pd(PPh₃)₄ (0.00015 mol) in methylbenzene (5ml) was stirred and refluxed for 3 hours. K₂CO₃ 10% was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (0.7g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 µm). Two fractions (F1 and F2) were collected and their solvents were evaporated. Yield: 0.27g (F1, starting material) and 0.14g (F2). F2 was crystallized from pentane and petroleum ether. The precipitate was filtered off and dried. Yield: 0.08g of compound (27) (17%); mp. 110°C.

o) Preparation of



(compound 28)

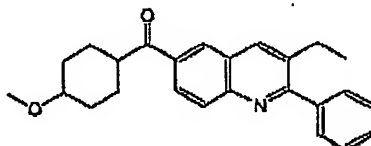
cis

A mixture of compound (4) (0.001507 mol), tributylethenylstannane (0.002260 mol) and Pd(PPh₃)₄ (0.000151 mol) in dioxane (5ml) was stirred at 80°C for 8 hours. Water was added. The mixture was filtered over celite, washed with EtOAc and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (0.65g) was purified by column chromatography over

- 53 -

silica gel (eluent: cyclohexane/EtOAc 90/10; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.07g of compound (28) (14%); mp. 108°C.

p) Preparation of

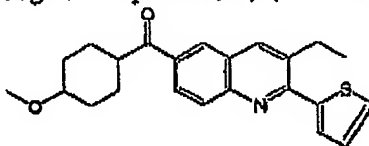


(compound 29)

trans

- 5 A mixture of compound (5) (0.001507 mol), triphenyl(phenylmethyl)stannane (0.002260 mol) and Pd(PPh₃)₄ (0.000151 mol) in dioxane (5ml) was stirred at 80°C for 8 hours. Water was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.4g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc
- 10 96/4; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue (0.38g) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.16g of compound (29) (28%); mp. 112°C.

q) Preparation of

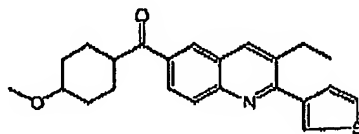


(compound 30)

cis

- A mixture of compound (4) (0.001507 mol), tributyl-2-thienylstannane (0.00226 mol) and Pd(PPh₃)₄ (0.0001507 mol) in dioxane (5ml) was stirred at 80°C for 8 hours.
- 15 K₂CO₃ 10% was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.7g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μ m). The pure fractions were collected and the solvent was evaporated. The residue (0.65g) was crystallized from diethyl ether. The
- 20 precipitate was filtered off and dried. Yield: 0.35g of compound (30) (61%); mp. 142°C.

r) Preparation of



(compound 31)

cis

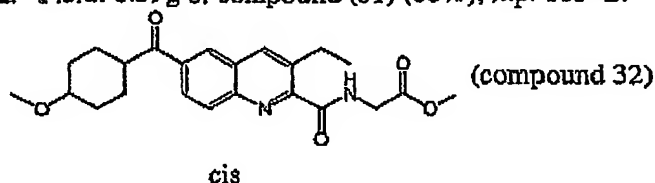
A mixture of compound (4) (0.0015 mol), 3-thienyl boronic acid (0.00226 mol), Pd(PPh₃)₄ (0.00015 mol) and dioxane was stirred and refluxed for 24 hours. K₂CO₃

- 54 -

10% was added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (0.8g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 15-40 μm). The pure fractions were collected and the solvent was evaporated.

- 5 The residue (0.4g, 70%) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.39g of compound (31) (68%); mp. 113°C.

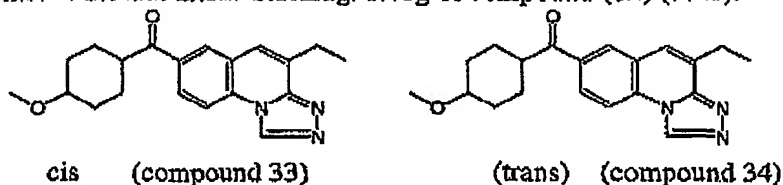
s) Preparation of



A mixture of compound (4) (0.003 mol), glycine methyl ester monohydrochloride (0.0066 mol) and $\text{Pd}(\text{PPh}_3)_4$ (0.0003 mol) in Et_3N (2ml) and toluene (10ml) was stirred at 100°C under 5 bar pressure of CO for 8 hours, filtered over celite, washed with

10 CH_2Cl_2 and evaporated. The residue (2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 80/20; 75-35 μm). One fraction was collected and the solvent was evaporated. This fraction (1g 80%) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.46g of compound (32) (37%).

t) Preparation of

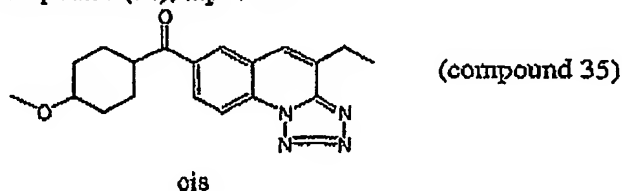


- 15 A mixture of compound (4) (0.003 mol) and hydrazinecarboxaldehyde (0.0045 mol) in 1-butanol (15ml) was stirred and refluxed overnight, poured out into water and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 95/5/0.1; 15-40 μm). Two fractions (F1 and F2) were collected and their solvents were evaporated. Yield: 0.3g F1 and 0.3g F2.

- 20 F1 was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.102g of compound (33); mp. 224°C.

F2 was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.2g of compound (34); mp. 185°C.

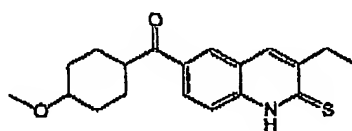
u) Preparation of



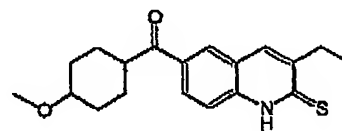
- 55 -

A mixture of compound 4 (0.015 mol) and NaN_3 (0.045 mol) in DMF (50ml) was stirred at 140°C for 2 hours. K_2CO_3 10% was added and the mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (6g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 60/40; 15-40 μm). The first fraction was collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 1.26g of compound (35) (24%); mp. 160°C .

v) Preparation of



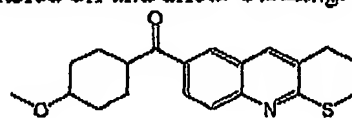
CIS
(compound 36)



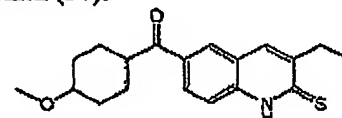
TRANS
(compound 37)

A mixture of compound (4) (0.009 mol) and thiourea (0.0099 mol) in ethyl alcohol (30ml) was stirred and refluxed for 12 hours and a solution of KOH (0.0149 mol) in H_2O (5ml) was added slowly. The mixture was stirred and refluxed for 1 hour, poured out into water and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (cyclohexane/EtOAc 70/30; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.1g of F1 (37%) and 0.4g of F2 (13%). F1 was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: compound (36). F2 was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: compound (37).

w) Preparation of



CIS
(compound 38)



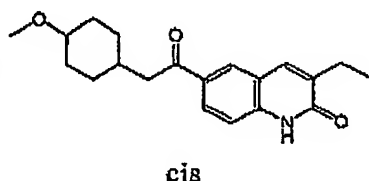
TRANS
(compound 39)

CH_3I (0.0034 mol) was added slowly at room temperature to a solution of compound (36) (0.0015 mol), compound (37) (0.0015 mol) and K_2CO_3 (0.0034 mol) in acetone (15ml). The mixture was stirred at room temperature for 8 hours. Water was added and the mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.6g F1 (57%), and 0.18g F2 (17%). F1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.28g compound (38) (27%). F2 was crystallized from

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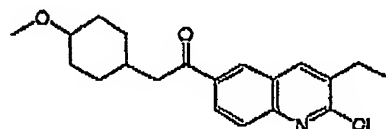
diethyl ether. The precipitate was filtered off and dried. Yielding: 0.065g of compound (39) (6%).

x) Preparation of



(compound 40)

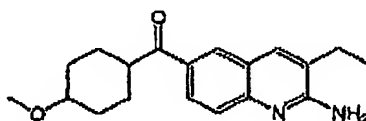
A mixture of



compound (41) prepared

according to example B3.b (0.0014 mol) in HCl 3N (5ml) and THF (5ml) was stirred and refluxed for a weekend, then poured out into H₂O, basified with K₂CO₃ and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. Yielding: 0.5g of F. This fraction F was crystallized from 2-propanone. The precipitate was filtered off and dried. Yielding: 0.35g of compound (40) (74%).

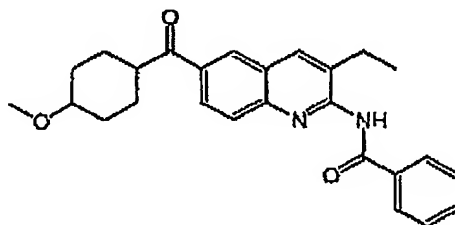
y) Preparation of



(compound 188)

A mixture of compound (5) (0.045 mol), acetamide (0.90013 mol) and K₂CO₃ (0.225 mol) was stirred and refluxed at 200°C for 2 hours, cooled at room temperature, poured out into H₂O/CH₂Cl₂; and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated till dryness. The residue (14.4 g) was crystallized from CH₃OH. The precipitate was filtered off and dried. The filtrate was evaporated. The residue (11.27g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 96/4/0.1; 15-35μm). The pure fractions were collected and the solvent was evaporated. Yielding: 4.2 g of compound (188) (65%).

z) Preparation of

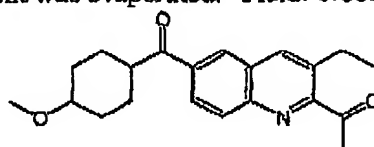


(compound 248)

- 57 -

A mixture of compound (188) (0.00032 mol), benzoic acid (1.5 equiv., 0.00048 mol), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide .HCl (1:1) (1.5 equiv., 0.00048 mol), N-hydroxybenzotriazole (1.5 equiv., 0.00048 mol) and Et₃N (1 equiv., 0.00032 mol) in CH₂Cl₂ (2ml) was stirred at room temperature for 15 hours. The solvent was
 5 evaporated. The residue was purified by HPLC and the product fractions were collected and the solvent was evaporated. Yield: 0.066 g of compound (205) (49.50%).

aa) Preparation of

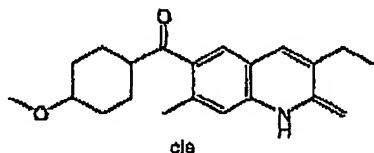


(compound 6)

trans

A mixture of interm. 20 (0.001507 mol) in HCl 3N (10ml) and THF (10ml) was stirred at room temperature for 8 hours, basified with K₂CO₃ 10% and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was
 10 evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 85/15; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.4g) was crystallized from petroleum ether. The precipitate was filtered off and dried. Yield: 0.3g of compound (6) (58%); mp. 108°C.

ab) Preparation of



(compound 419)

cis

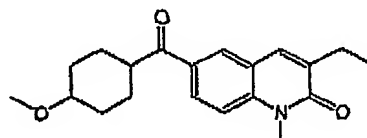
A mixture of compound 213 (prepared according to B4) (0.00305 mol) and CH₃ONa (30% in CH₃OH) (0.00916 mol) in CH₃OH (25ml) was stirred and refluxed for 15 hours then cooled to room temperature, poured out into H₂O and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was
 20 evaporated till dryness. The residue (1.1g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 40/60; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.3g F1 and 0.5g F2 (50%) F2 was crystallized from diethyl ether/petroleum ether. The precipitate was filtered off and dried. Yielding: 0.26g F1 was crystallized from pentane. The precipitate was filtered off and dried. Yielding: 0.19g. This fraction was purified by column chromatography
 25 over silica gel (eluent: CH₂Cl₂/CH₃OH; 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.11g. This fraction was purified by column chromatography over kromasil (eluent: CH₃OH/H₂O; 70/30). The pure

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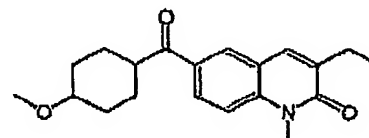
fractions were collected and the solvent was evaporated. Yielding: 0.09g. (9%) This fraction was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.08g of compound 419 (8%).

Example B5

Preparation of



cis (compound 42)

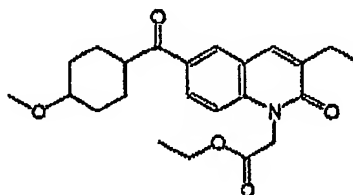


(trans) (compound 43)

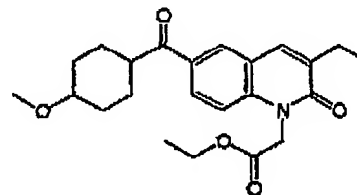
- 5 Iodomethane (0.00456 mol) was added at 5°C to a mixture of compound (9) (0.0019 mol), compound (8) (0.0019 mol) and tBuOK (0.00456 mol) in THF (30ml) under N₂ flow. The mixture was stirred at room temperature overnight, poured out into H₂O and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over
10 silica gel (eluent: cyclohexane/EtOAc 65/35; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yield: 0.35g of compound (42) (30%; mp. 125°C) and 0.35g of compound (43) (30%; mp. 116°C).

Example B6

a) Preparation of



cis (compound 44)

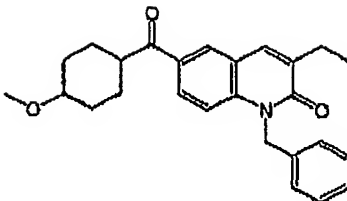


(trans) (compound 45)

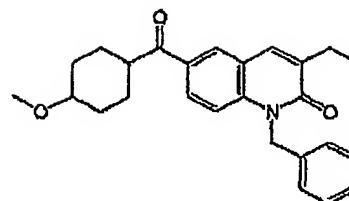
- 15 NaH 60% (0.01068 mol) was added at 0°C under N₂ flow to a mixture of compound (8) and compound (9) (0.0089 mol). The mixture was stirred for 30 minutes. Ethyl bromoacetate (0.01068 mol) was added at 0°C. The mixture was stirred at room temperature for 1 hour, hydrolyzed with water and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent:
20 cyclohexane/EtOAc 60/40; 15-40 μm). The desired fractions (F1-F4) were collected and the solvent was evaporated. Yield: 0.11g F1; 0.13g F2; 0.75g F3 and 0.8g F4. F3 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: compound (44); mp. 152°C.
25 F4 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: compound (45); mp. 147°C.

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b) Preparation of



cis (compound 46)



(trans) (compound 47)

Bromomethylbenzene (0.007 mol) was added dropwise at 0°C under N₂ flow to a solution of compound (8) and compound (9) (0.0064 mol) and NaH 60% (0.007 mol) in DMF (40ml). The mixture was stirred at room temperature for 1 hour, hydrolyzed with water and extracted with EtOAc. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc 70/30; 15-40 μm). The desired fractions (F1-F4) were collected and the solvent was evaporated. Yield: 0.15g F1, 0.1g F2, 0.6g F3 (23%) and 0.8g F4.

F3 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.13g of compound (46); mp. 137°C.

F4 was crystallized from DIPE and petroleum ether. The precipitate was filtered off and dried. Yield: compound (47); mp. 130°C.

Example B7

a) 3-Chlorobenzenecarboperoxoic acid (0.088 mol) was added at 0°C to a solution of compound (48) (prepared according to example B2) (0.044 mol) in CH₂Cl₂ (200ml) and the mixture was stirred at room temperature for 12 hours. The mixture was washed with K₂CO₃ 10%. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue was recrystallized from (C₂H₅)₂O. Yield : 8.2g of

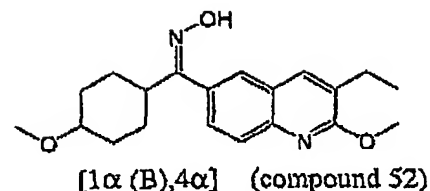
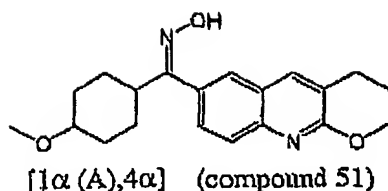
cyclohexyl(3-methyl-6-quinolinyl)methanone,1-oxide (compound 49) (69%).

b) 4-Methyl benzenesulfonyl chloride (0.043 mol) was added to a solution of compound (49) (0.028 mol) in K₂CO₃ (400ml) and CH₂Cl₂ (400ml) and the mixture was stirred at room temperature for 1 hour. The mixture was extracted with CH₂Cl₂. The organic layer was dried (MgSO₄), filtered off and evaporated. The residue was recrystallized from (C₂H₅)₂O. Yield : 6.64g of 6-(cyclohexylcarbonyl)-3-methyl-2(1H)-quinolinone (compound 50) (85%); mp. 256.1°C.

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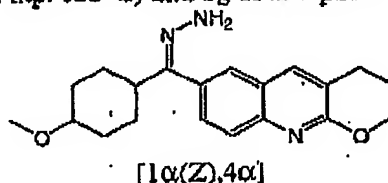
Example B8

a) Preparation of



A mixture of compound (7) (0.0229 mol), hydroxylamine (0.0252 mol) and *N,N*-diethylethanamine (0.0252 mol) in ethanol (100ml) was stirred and refluxed for 6 hours, poured out into water and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was crystallized from CH_3CN . The precipitate was filtered off and dried. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 80/20; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yielding: 2.8g of compound (44) (36%; mp. 133°C) and 3g of compound (45) (38%; mp. 142°C).

b) Preparation of

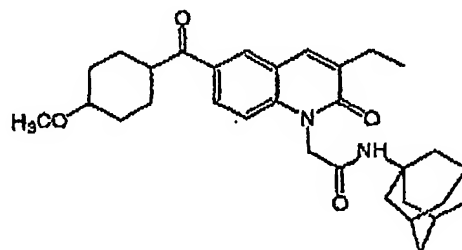


(compound 53)

- 10 Hydrazine (0.41 mol) was added at room temperature to a solution of compound (7) (0.015 mol) in ethanol (75ml). The mixture was stirred and refluxed for 1 night, poured out into water and extracted with CH_2Cl_2 . The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 98/2/0.1).
- 15 The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.8g of compound (53) (15%); mp. 110°C.

Example B9

Preparation of



(compound 520)

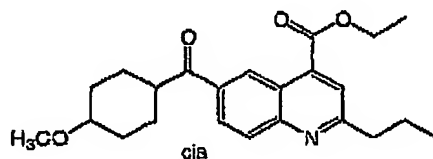
- 20 Procedure for compounds 400, 401, 402, 403, 404 and 405. A mixture of interm. 21 (prepared according to A11) (0.000269 mol), amantadine hydrochloride (0.000404 mol; 1.5 eq.), *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine

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hydrochloride (0.000404 mol; 1.5 equiv.), 1-hydroxy-1*H*-benzotriazole (0.000404 mol; 1.5 equiv.) and Et₃N (0.000269 mol) in CH₂Cl₃ (2 ml) was stirred at room temperature for 12 hours. The solvent was evaporated. The residue was purified by HPLC. The product fractions were collected and the solvent was evaporated. Yield: 0.063 g of ..
 5 compound 520 (46.37%).

Example B10

Preparation of

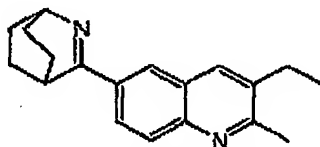


(compound 233)

A mixture of intermediate 27 (0.0026 mol) and intermediate 26 (0.0026 mol) in EtOH (380 ml) and H₂SO₄ conc. (19 ml) was stirred and refluxed for 15 hours, then cooled to room temperature, poured out into ice water, basified with K₂CO₃ and extracted with
 10 EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (17.9 g) was purified by column chromatography over silica gel (eluent: cyclohexane/EtOAc; 80/20; 15-35 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.85 g of F1, 1.1 g F2 and 11.5 g of F3. F1 and F2 were crystallized separately from petroleum ether. The precipitate was filtered
 15 off and dried. Yielding: 0.34 g of compound 233.

Example B11

Preparation of

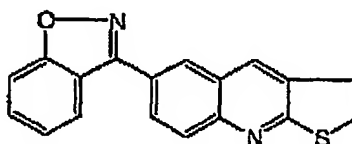


(compound 511)

A mixture of compound 22 (prepared according to B4) (0.004 mol) in HCl (3N) (20 ml) and THF (20 ml) was stirred and refluxed for 8 hours, poured out on ice, basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄),
 20 filtered, and the solvent was evaporated. The residue (1.2 g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH; 93/7/0.5; 15-40 μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.5 g F1 (41%) and 0.4 g of F2. F1 was crystallized from petroleum ether. The precipitate was filtered off and dried. Yielding: 0.17 g of compound 511 (14%).

Example B12

Preparation of



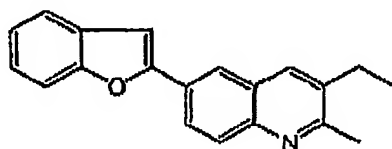
(compound 514)

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- A mixture of compound 524 (prepared according to B9a) (0.0018 mol) and KOH 85% (0.0094 mol) in EtOH (15ml) was stirred and refluxed for 24 hours, poured out into H₂O and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/Cyclohexane 80/20; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.35g F1 (64%) and 0.17g (SM) F1 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.33g of compound 514 (60%) (mp.:185°C).

Example B13

Preparation of

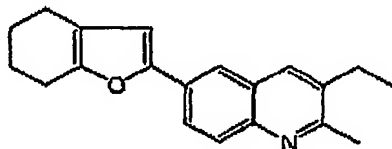


(compound 515)

- A mixture of interm. 28 (0.019 mol), 2-benzofuranylboronic acid (0.028 mol), Pd(PPh₃)₄ (0.001 mol) and BHT (a few quantity) in dioxane (25ml) and Na₂CO₃ [2] (25ml) was stirred and refluxed for 8 hours and extracted with EtOAc. The aqueous layer was basified with NH₄OH and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (3.6g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.8g (33%). This fraction was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.39g of compound 515 (7%) (mp.:134°C).

20 Example B14

Preparation of



(compound 526)

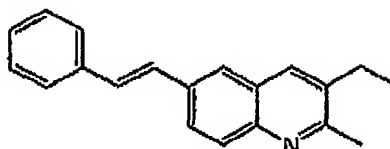
- Triethylsilane (0.0012 mol) was added slowly at room temperature to a solution of interm. 32 (0.004 mol) in CF₃COOH (5ml) and AcOH (10ml). NaBH₄ (0.0012 mol) was added portionwise under N₂ flow. The mixture was stirred at room temperature for 8 hours, poured out on ice, basified with K₂CO₃ and extracted with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 99/1; 15-40μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.5g F1 (43%) and 0.4g F2. F1 was dissolved in iPrOH.

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HCl/iPrOH (1 eq) were added. The precipitate was filtered off and dried; Yielding: 0.32g of compound 526 (mp.: 248°C).

Example B15

Preparation of

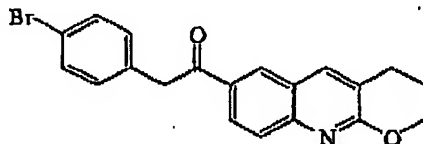


(compound 471)

A mixture of interm. 33 (0.082 mol) and 3-chloro-2-ethyl-2-butenal (0.098 mol) in AcOH (200ml) was stirred and refluxed for 8 hours. The solvent was evaporated till dryness. The residue was dissolved in CH₂Cl₂ and washed with K₂CO₃ 10%. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (27g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/EtOAc 95/5 to 92/8; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 0.7g of F1 and 5.3g F2. F1 was crystallized from 2-propanone/diethyl ether. The precipitate was filtered off and dried. Yielding: 0.25g of compound 471 (2%) (mp.: 140°C).

Example B16

Preparation of



(compound 498)

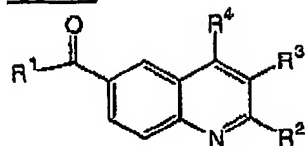
nBuLi (0.0417 mol) was added dropwise at -78°C to a solution of interm. 35 (prepared according to A17.b) (0.0379 mol) in THF (200ml) under N₂ flow. The mixture was stirred for 30 minutes. A solution of 4-bromo-N-methoxy-N-methylbenzeneacetamide (0.0568 mol) in THF (100ml) was added dropwise at -78°C. The mixture was stirred from -78°C to 0°C, poured out into H₂O and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated till dryness. The residue (20.9g) was purified by column chromatography over silica gel (eluent: toluene/EtOAc 60/40 to 50/50; 15-35μm). Two fractions were collected and the solvent was evaporated. Yielding: 4g of fraction 1 and 4g of fraction 2 (28%). Fraction 2 was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 1g compound 528 (m.p. 195°C).

25

Tables 1 to 8 list the compounds of formula (I-A) and (I-B) which were prepared according to one of the above examples.

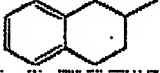
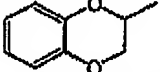
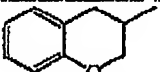
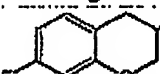
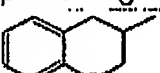
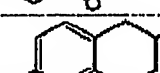
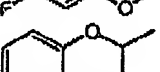
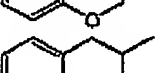
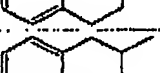
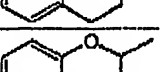
- 64 -

Table 1

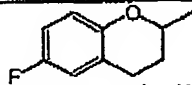

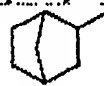
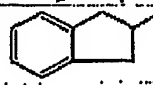
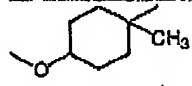
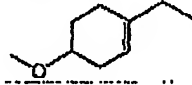


| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|---------|---------|------------------|----------------|----------------|---|-----------------|
| 54 | B2 | Cl | ethyl | H | | - |
| 3 | B3a | Cl | ethyl | H | | mp. 145°C |
| 55 | B3b | Cl | ethyl | H | | mp. 131°C |
| 56 | B3b | Cl | ethyl | H | | mp. 104°C |
| 57 | B3b | Cl | ethyl | H | phenylethyl | mp. 100°C |
| 58 | B3b | Cl | ethyl | H | | mp. 126°C |
| 59 | B3b | Cl | ethyl | H | | mp. 150°C |
| 60 | B3b | Cl | ethyl | H | | mp. 138°C |
| 61 | B3b | OCH ₃ | ethyl | H | | - |
| 62 | B3b | OCH ₃ | ethyl | H | | mp. 130°C |
| 63 | B3b | OCH ₃ | ethyl | H | | mp. 116°C |
| 64 | B3b | Cl | ethyl | H | -(CH ₂) ₂ -O-CH ₃ | mp. 82°C |
| 65 | B3b | OCH ₃ | ethyl | H | 1-methylcyclohexyl | mp. 82°C |
| 66 | B3b | OCH ₃ | ethyl | H | 3-methoxycyclohexyl | trans; mp. 94°C |




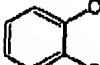




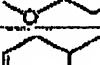
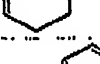
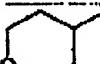

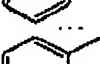
- 65 -

| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|------------------|----------------|----------------|--|---------------------|
| 67 | B3b | OCH ₃ | ethyl | H | 3-methoxycyclohexyl | cis; mp. 108°C |
| 68 | B3b | OCH ₃ | ethyl | H | 4-(methylethoxy)- cyclohexyl | (A), mp. 82°C |
| 69 | B3b | OCH ₃ | ethyl | H | 4-[C(CH ₃) ₃]cyclohexyl | cis; mp. 92°C |
| 70 | B3b | OCH ₃ | ethyl | H | 4-[C(CH ₃) ₃]cyclohexyl | trans; mp. 108°C |
| 71 | B3b | OCH ₃ | ethyl | H | 4-methylcyclohexyl | (B), mp. 92°C |
| 72 | B3b | OCH ₃ | ethyl | H | 4-methylcyclohexyl | (A), mp. 80°C |
| 2 | B2 | Cl | ethyl | H | CH ₂ -CH(CH ₃) ₂ | mp. 82°C |
| 73 | B3b | Cl | ethyl | H | -CH ₂ -O-C ₂ H ₅ | mp. 82°C |
| 48 | B2 | H | methyl | H | cyclohexyl | |
| 74 | B4 | I | ethyl | H |  | |
| 75 | B4 | I | ethyl | H |  | mp. 124°C |
| 76 | B4 | I | ethyl | H |  | mp. 138°C |
| 77 | B4 | I | ethyl | H |  | mp. 120°C |
| 78 | B4 | CN | ethyl | H |  | mp. 128°C |
| 79 | B4 | CN | ethyl | H |  | mp. 136°C |
| 80 | B4 | CN | ethyl | H |  | mp. 120°C |
| 81 | B4 | CN | ethyl | H |  | mp. 139°C |
| 82 | B4 | methyl | ethyl | H |  | mp. 106°C |
| 83 | B4 | methyl | ethyl | H |  | mp. 149°C |

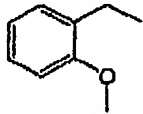

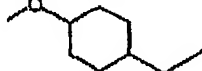
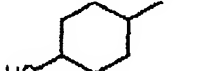

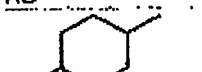
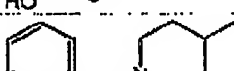


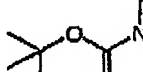



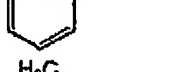
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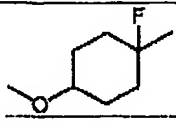
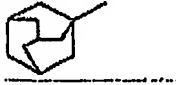
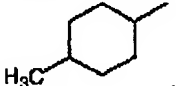
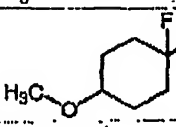
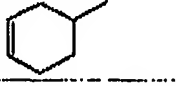
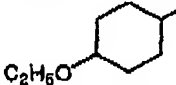
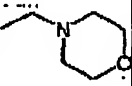
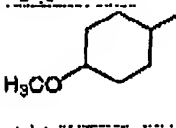
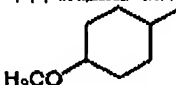
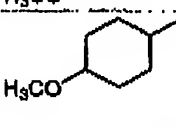
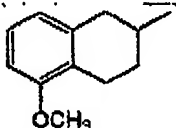
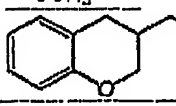
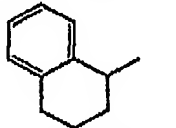
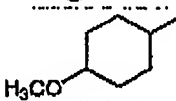
| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|----------------------------------|----------------|-----------------|--|---------------------------------|
| 84 | B4 | methyl | ethyl | H |  | mp. 118°C |
| 85 | B4 | methyl | ethyl | H |  | mp. 180°C |
| 86 | B4 | methyl | ethyl | H | phenylethyl | mp. 53°C |
| 87 | B4 | methyl | ethyl | H |  | mp. 87°C |
| 88 | B4 | methyl | ethyl | H | -CH ₂ -CH(CH ₃) ₂ | mp. 68°C |
| 89 | B4 | methyl | ethyl | H |  | mp. 120°C |
| 31 | B4 | 3-thiazolyl | ethyl | H | 4-methoxycyclohexyl | cis; 113°C |
| 90 | B3b | OCH ₃ | H | H | 4-methoxycyclohexyl | trans, mp. 126°C |
| 91 | B3b | OCH ₃ | H | H | 4-methoxycyclohexyl | cis, mp. 100°C |
| 92 | B3b | OCH ₃ | H | CH ₃ | 4-methoxycyclohexyl | cis; mp. 120°C |
| 93 | B3b | OCH ₃ | H | CH ₃ | 4-methoxycyclohexyl | trans; mp. 111°C |
| 94 | B3b | OCH ₃ | methyl | H | 4-methoxycyclohexyl | cis, mp. 96°C |
| 95 | B3b | OCH ₃ | phenyl | H | 4-methoxycyclohexyl | cis; HCl (1:1), mp. 138°C |
| 96 | B3b | OCH ₃ | propyl | H | 4-methoxycyclohexyl | trans; mp. 118°C |
| 97 | B3b | OCH ₃ | propyl | H | 4-methoxycyclohexyl | cis; mp. 108°C |
| 98 | B3b | OCH ₃ | methyl | H | 4-methoxycyclohexyl | cis; mp. 104°C |
| 99 | B4 | N(CH ₃) ₂ | ethyl | H |  | (B); mp. 102°C |
| 100 | B3b | Cl | ethyl | H |  | mp. 114°C |
| 101 | B4 | methyl | ethyl | H | 4-butoxycyclohexyl | cis; mp. 86°C |

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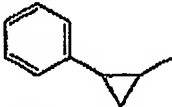
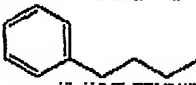
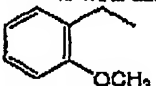
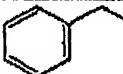
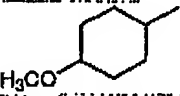
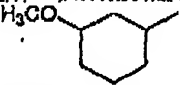
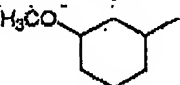
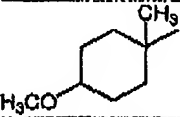
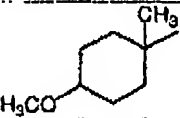
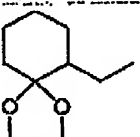
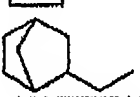
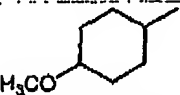
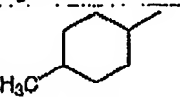
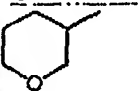
| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|----------------------------------|----------------|----------------|--|---------------------|
| 102 | B3b | Cl | ethyl | H |  | mp. 78°C |
| 103 | B3b | Cl | ethyl | H |  | mp. 91°C |
| 104 | B4 | N(CH ₃) ₂ | ethyl | H |  | mp. 103°C |
| 105 | B4 | N(CH ₃) ₂ | ethyl | H |  | mp. 170°C |
| 106 | B3b | Cl | ethyl | H |  | mp. 137°C |
| 107 | B3b | Cl | ethyl | H |  | mp. 137°C |
| 108 | B4 | methyl | ethyl | ethyl | 4-methoxycyclohexyl | cis; mp. 91°C |
| 109 | B4 | methyl | ethyl | H | 4-ethoxycyclohexyl | trans; mp. 150°C |
| 110 | B4 | methyl | ethyl | H |  | mp. 90°C |
| 111 | B4 | methyl | ethyl | H |  | mp. 94°C |
| 112 | B4 | methyl | ethyl | H |  | mp. 176°C |
| 113 | B4 | methyl | ethyl | H |  | mp. 106°C |
| 114 | B4 | propyl | H | H | 4-methoxycyclohexyl | cis; mp. 74°C |
| 115 | B4 | methyl | ethyl | H | 4-ethoxycyclohexyl | cis; mp. 108°C |
| 116 | B4 | methyl | ethyl | H |  | mp. 110°C |
| 117 | B3b | Cl | ethyl | H |  | mp. 124°C |
| 118 | B3b | Cl | ethyl | H |  | mp. 107°C |

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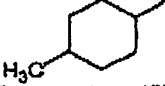
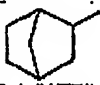
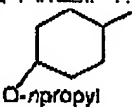

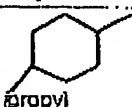
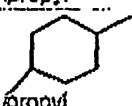
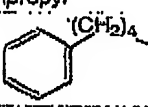
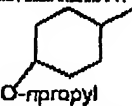
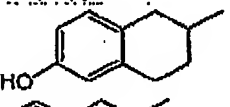
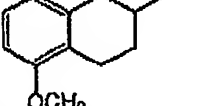
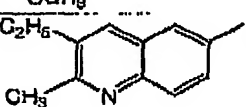
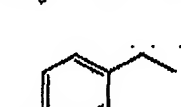
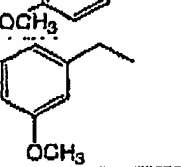
| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|---------|---------|----------------|----------------|----------------|--|------------------------------------|
| 119 | B3b | Cl | ethyl | H |  | mp. 129°C |
| 120 | B4 | methyl | ethyl | H |  | mp. 106°C |
| 41 | B3b | Cl | ethyl | H |  | trans; mp. 157°C |
| 182 | B3b | methyl | ethyl | H |  | cis; mp. 170°C |
| 183 | B3b | methyl | ethyl | H |  | trans; mp. 144°C |
| 184 | B3b | methyl | ethyl | H |  | mp. 138°C |
| 185 | B3b | Cl | ethyl | H |  | mp. 120°C |
| 186 | B3b | Cl | ethyl | H |  | |
| 187 | B3b | methyl | ethyl | H |  | mp. 162°C |
| 216 | B4 | CC≡N | ethyl | H |  | mp.: 160°C |
| 217 | B4 | methyl | ethyl | H |  | .ethanedioate (1:1); mp.: 143°C |
| 218 | B4 | I | ethyl | H |  | mp.: 102°C |
| 219 | B4 | CC≡N | ethyl | H |  | mp.: 115°C |
| 220 | B4 | Cl | ethyl | H |  | (A); mp.: 107°C |

| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|----------------|---|--------------------------------------|--|-------------------------------------|
| 221 | B4 | Cl | ethyl | H |  | (B); mp.:113°C |
| 222 | B4 | I | ethyl | H |  | mp.:206°C |
| 223 | B4 | Cl | ethyl | H |  | (trans); mp.:117°C |
| 224 | B4 | methyl | ethyl | H |  | (A); mp.:103°C |
| 225 | B2 | Cl | ethyl | H |  | mp.:94°C |
| 226 | B3b | Cl | ethyl | H |  | (trans); mp.:157°C |
| 227 | B3c | methoxy |  | H |  | mp.:204°C |
| 228 | B4 | Cl | ethyl | H |  | (A); mp.:136°C |
| 229 | B3b | n-propyl | H | H |  | (trans);.HCl (1:1); mp.:150°C |
| 230 | B3b | Cl | ethyl | H |  | mp.:116°C |
| 231 | B3b | Cl | ethyl | H |  | mp.:120°C |
| 232 | B3b | Cl | ethyl | H |  | mp.:112°C |
| 233 | B10 | i-propyl | H | C(=O)O-C ₂ H ₅ |  | (cis); mp.:91°C |

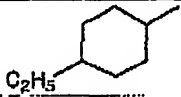
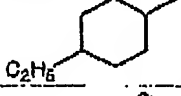
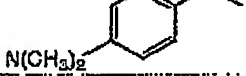


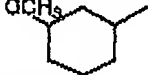


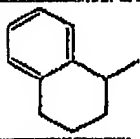
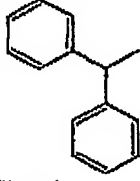
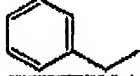
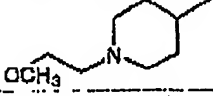
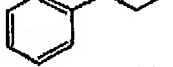
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| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|---------|---------|------------------------|----------------|----------------|--|------------------------|
| 234 | B4 | methyl | ethyl | H |  | mp.: 122°C |
| 235 | B4 | methyl | ethyl | H |  | mp.: 106°C |
| 236 | B4 | methyl | ethyl | H |  | mp.: 104°C |
| 237 | B4 | methyl | ethyl | H |  | mp.: 90°C |
| 238 | B4 | methyl | H | H |  | (cis); mp.: 80°C |
| 239 | B3b | Cl | ethyl | H |  | (trans); mp.: 126°C |
| 240 | B3b | Cl | ethyl | H |  | (cis); mp.: 128°C |
| 241 | B4 | methyl | ethyl | H |  | (A); mp.: 90°C |
| 242 | B4 | methyl | ethyl | H |  | (B); mp.: 110°C |
| 243 | B3b | Cl | ethyl | H |  | mp.: 134°C |
| 244 | B3b | Cl | ethyl | H |  | mp.: 127°C |
| 245 | B4 | NHC(=O)NH ₂ | ethyl | H |  | (cis); mp.: 176°C |
| 246 | B4 | methyl | ethyl | H |  | (B) |
| 247 | B3b | Cl | ethyl | H |  | mp.: 92°C |

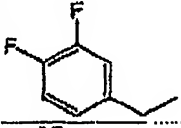
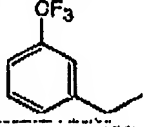
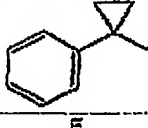
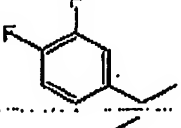
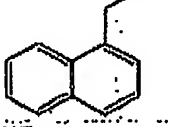
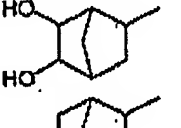
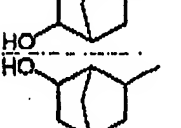
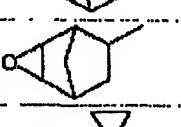
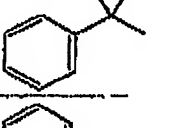
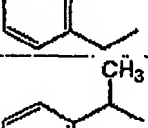
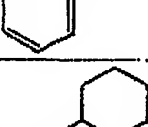
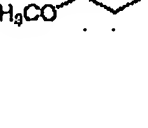

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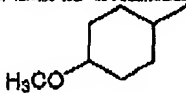
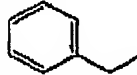
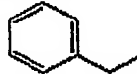
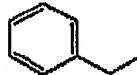
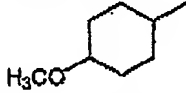
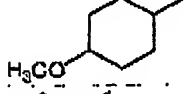
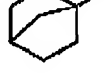
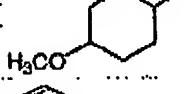
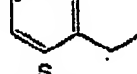

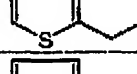
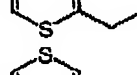


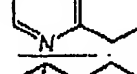

| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|---------|---------|----------------|----------------|----------------|--|--------------------|
| 248 | B4 | methyl | ethyl | H |  | (A); mp.:80°C |
| 249 | B3b | Cl | ethyl | H |  | (B); mp.:138°C |
| 250 | B4 | methyl | ethyl | H |  | (trans); mp.:118°C |
| 251 | B4 | methyl | ethyl | H |  | (B); HCl(1:1) |
| 252 | B3b | Cl | ethyl | H |  | (A) |
| 253 | B3b | Cl | ethyl | H |  | (B) |
| 254 | B3b | methyl | ethyl | H |  | mp.:74°C |
| 255 | B4 | methyl | ethyl | H |  | (cis); mp.:68°C |
| 256 | B4 | methyl | ethyl | H |  | mp.:210°C |
| 257 | B4 | methyl | ethyl | H |  | mp.:113°C |
| 258 | B4 | methyl | ethyl | H |  | mp.:92°C |
| 259 | B3b | methyl | ethyl | H |  | mp.:115°C |
| 260 | B3b | methyl | ethyl | H |  | mp.:60°C |


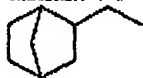
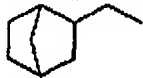
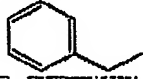


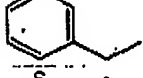

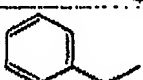
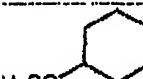



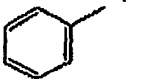

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| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|--|----------------|----------------|--|-------------------------------|
| 261 | B3b | Cl | ethyl | H |  | (A); mp.:86°C |
| 262 | B3b | Cl | ethyl | H |  | (B); mp.:101°C |
| 263 | B3b | methyl | ethyl | H |  | mp.:130°C |
| 264 | B3b | Cl | ethyl | H |  | (A); mp.:124°C |
| 265 | B3b | Cl | ethyl | H |  | (B); mp.:126°C |
| 266 | B4 | N(CH ₃) ₂ | ethyl | H |  | (trans); mp.:102°C |
| 267 | B4 | N(CH ₃) ₂ | ethyl | H |  | (cis);.HCl(1:1); mp.:170°C |
| 268 | B4 | methyl | ethyl | H |  | (A);.HCl(1:1); mp.:206°C |
| 269 | B4 | methyl | ethyl | H |  | mp.:104°C |
| 270 | B3b | methyl | ethyl | H |  | mp.:117°C |
| 271 | B4 | NEC ₂ H ₅ OCH ₃ | ethyl | H |  | |
| 272 | B4 | methyl | ethyl | H |  | |
| 273 | B4 | NH ₂ | ethyl | H |  | |

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| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|----------------|--|----------------|--|-----------------------|
| 274 | B3b | Cl | ethyl | H |  | - |
| 275 | B3b | Cl | ethyl | H |  | mp.:99°C |
| 276 | B3b | Cl | ethyl | H |  | mp.:95°C |
| 277 | B4 | methyl | ethyl | H |  | mp.:105°C |
| 278 | B3b | Cl | ethyl | H |  | mp.:141°C |
| 279 | B4 | Cl | ethyl | H |  | mp.:168°C |
| 280 | B4 | Cl | ethyl | H |  | - |
| 281 | B4 | Cl | ethyl | H |  | mp.:140°C |
| 282 | B4 | Cl | ethyl | H |  | mp.:169°C |
| 283 | B4 | methyl | ethyl | H |  | mp.:96°C |
| 284 | B3b | Cl | CH ₂ N(CH ₃) ₂ | H |  | mp.:115°C |
| 285 | B4 | methyl | ethyl | H |  | mp.:133°C |
| 286 | B4 | methyl | CH ₂ OCH ₃ | H |  | (trans); mp.:106°C |

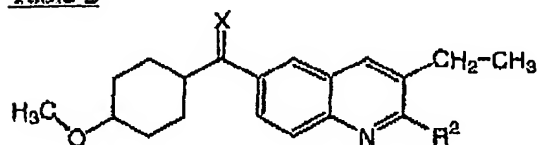
| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|------------|------------|-----------------|--|----------------|--|-----------------------|
| 287 | B4 | methyl | CH ₂ N(CH ₃) ₂ | H |  | (cis); mp.:110°C |
| 288 | B3b | Cl | <i>n</i> -propyl | H |  | mp.:110°C |
| 289 | B4 | NH ₂ | ethyl | H |  | mp.:218°C |
| 290 | B4 | methyl | <i>n</i> -propyl | H |  | mp.:90°C |
| 291 | B3b | Cl | <i>n</i> -propyl | H |  | (cis); mp.:128°C |
| 292 | B3b | Cl | <i>n</i> -propyl | H |  | (trans); mp.:104°C |
| 293 | B3b | Cl | ethyl | H |  | mp.:106°C |
| 294 | B4 | methyl | <i>n</i> -propyl | H |  | (cis); mp.:94°C |
| 295 | B4 | methyl | CH ₂ N(CH ₃) ₂ | H |  | mp.:83°C |
| 296 | B3b | Cl | ethyl | H |  | mp.:99°C |
| 297 | B3b | Cl | ethyl | H |  | mp.:110°C |
| 298 | B4 | methyl | ethyl | H |  | mp.:93°C |
| 299 | B4 | methyl | ethyl | H |  | mp.:105°C |
| 300 | B4 | methyl | ethyl | H |  | mp.:114°C |
| 301 | B3b | methyl | ethyl | H |  | mp.:143°C |
| 302 | B4 | methoxy | ethyl | H |  | mp.:93°C |

| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|---------|---------|----------------|-------------------------------------|----------------|--|-------------------------|
| 303 | B4 | methyl | ethyl | H |  | mp.:82°C |
| 304 | B4 | n-butyl | ethyl | H |  | - |
| 305 | B3b | Cl | n-propyl | H |  | mp.:125°C |
| 306 | B1 | methyl | C(=O)OC ₂ H ₅ | H |  | mp.:136°C |
| 307 | B4 | methyl | n-propyl | H |  | mp.:81°C |
| 308 | B4 | methoxy | n-propyl | H |  | mp.:80°C |
| 309 | B4 | I | n-propyl | H |  | mp.:120°C |
| 310 | B3d | methyl | ethyl | H |  | .HCl(1:1); mp.:129°C |
| 311 | B3b | Cl | H | H |  | mp.:160°C |
| 312 | B3b | Cl | H | H |  | (trans); mp.:145°C |
| 313 | B3b | Cl | H | H |  | mp.:103°C |
| 314 | B4 | n-propyl | n-propyl | H |  | .HCl(1:1); mp.:150°C |
| 315 | B4 | n-propyl | ethyl | H |  | .HCl(1:1) |
| 316 | B4 | n-propyl | H | H |  | .HCl(1:1); mp.:140°C |
| 317 | B3b | Cl | H | H |  | mp.:168°C |

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| Co. no. | Ex. no. | R ² | R ³ | R ⁴ | R ¹ | physical data |
|---------|---------|----------------|----------------|----------------|---|-------------------------|
| 318 | B4 | methyl | n-propyl | H | | HCl(1:1); mp.: 200°C |
| 509 | B3b | Cl | ethyl | H | | - |
| 510 | B4 | methyl | ethyl | H | | H ₂ O(1:1) |
| 513 | B4 | methyl | ethyl | H | | - |
| 516 | B4 | Cl | ethyl | H | | mp.: 120°C |
| 517 | B4 | I | ethyl | H | CH ₂ CH(CH ₃) ₂ | - |
| 518 | B4 | Cl | ethyl | H | | - |
| 519 | B4 | Cl | ethyl | H | | (A+B) |
| 521 | B4 | I | ethyl | H | | - |
| 522 | B4 | methyl | ethyl | H | | (A) |
| 1 | B4 | methyl | ethyl | H | | (A) |
| 525 | B4 | Cl | ethyl | H | | - |
| 527 | B4 | F | ethyl | H | | mp.: 116°C |

Table 2

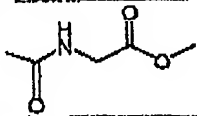
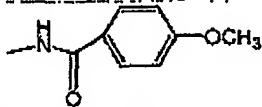
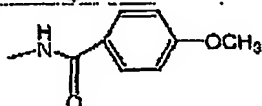
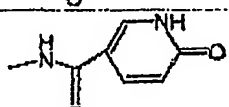
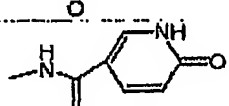


| Co. no. | Ex. no. | R ² | X | physical data |
|---------|---------|----------------|---|---------------|
|---------|---------|----------------|---|---------------|

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| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|--|---|-----------------------------|
| 5 | B3b | Cl | O | trans; mp. 120°C |
| 121 | B3b | 1-piperidinyl | O | cis; HCl (1:1) |
| 122 | B3b | 1-piperidinyl | O | trans; HCl (1:1); mp. 128°C |
| 123 | B3b | 4-thiomorpholinyl | O | cis; mp. 105°C |
| 124 | B3b | 4-thiomorpholinyl | O | trans; mp. 115°C |
| 125 | B3b | 4-morpholinyl | O | trans; mp. 118°C |
| 126 | B3b | 4-morpholinyl | O | cis; mp. 118°C |
| 127 | B3b | -N(CH ₃) ₂ | O | trans; mp. 96°C |
| 128 | B3b | -N(CH ₃) ₂ | O | cis; mp. 114°C |
| 4 | B3b | Cl | O | cis; mp. 123°C |
| 8 | B3c | OCH ₃ | O | trans; mp. 68°C |
| 7 | B3c | OCH ₃ | O | cis; mp. 116°C |
| 6 | B4 | acetyl | O | trans; mp. 108°C |
| 129 | B4 | acetyl | O | cis; mp. 106°C |
| 11 | B4 | NH-(CH ₂) ₂ -OCH ₃ | O | trans; mp. 107°C |
| 10 | B4 | NH-(CH ₂) ₂ -OCH ₃ | O | cis; mp. 115°C |
| 12 | B4 | NH-(CH ₂) ₂ -SCH ₃ | O | cis; mp. 120°C |
| 13 | B4 | NH-(CH ₂) ₂ -SCH ₃ | O | trans; mp. 125°C |
| 14 | B4 | -C≡C-Si(CH ₃) ₃ | O | cis; mp. 114°C |
| 16 | B4 | -C≡C-Si(CH ₃) ₃ | O | trans; mp. 108°C |
| 15 | B4 | -C≡CH | O | cis; mp. 132-133°C |
| 17 | B4 | -C≡CH | O | trans; mp. 128°C |
| 18 | B4 | -C≡C-CH ₂ OH | O | cis; mp. 113°C |
| 130 | B4 | -C≡C-CH ₂ OH | O | trans; mp. 108°C |
| 19 | B4 | F | O | cis; mp. 92-99°C |
| 20 | B4 | F | O | trans; mp. 114°C |
| 21 | B4 | I | O | cis; mp. 110°C |
| 22 | B4 | CN | O | cis; mp. 137-138°C |
| 26 | B4 | H | O | trans |
| 23 | B4 | -C(=O)-OCH ₃ | O | cis; mp. 91°C |
| 24 | B4 | -C(=O)-OCH ₃ | O | trans; mp. 99°C |
| 25 | B4 | H | O | cis; mp. 88°C |
| 27 | B4 | methyl | O | cis; mp. 110-112°C |

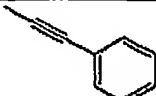
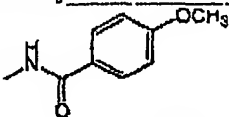
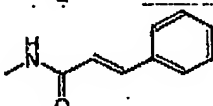
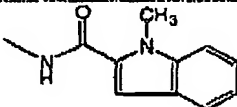
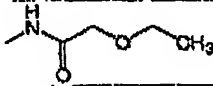
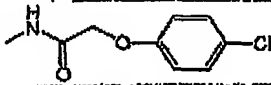
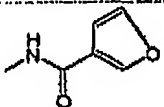

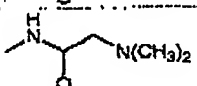
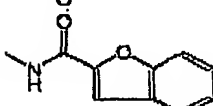
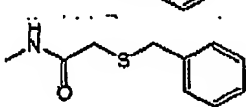
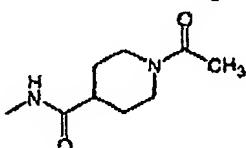
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| Co. no. | Ex. no. | R ² | X | physical data |
|---------|---------|---|------------------|--|
| 131 | B4 | methyl | O | trans; mp. 25°C |
| 28 | B4 | ethenyl | O | cis; mp. 108°C |
| 132 | B4 | ethenyl | O | trans; mp. 103°C |
| 29 | B4 | phenyl | O | trans; mp. 112°C |
| 30 | B4 | 2-thienyl | O | cis; 142°C |
| 133 | B4 | 2-thiazolyl | O | cis; 108°C |
| 134 | B4 | 2-furanyl | O | cis; mp. 105°C |
| 51 | B8a | OCH ₃ | N-OH | [1α(A),4α]; mp. 133°C |
| 52 | B8a | OCH ₃ | N-OH | [1α(B),4α]; mp. 142°C |
| 53 | B8b | OCH ₃ | NNH ₂ | [1α(Z),4α]; mp. 110°C |
| 135 | B4 | NH ₂ | O | cis; mp. 203°C |
| 136 | B4 | NH ₂ | O | trans; mp. 202°C |
| 137 | B4 | -C(=O)-OCH(CH ₃) ₂ | O | cis; mp. 105°C |
| 138 | B4 | -C(=O)-OCH(CH ₃) ₂ | O | trans; mp. 88°C |
| 38 | B4 | SCH ₃ | O | cis; mp. 124°C |
| 39 | B4 | SCH ₃ | O | trans; mp. 116°C |
| 32 | B4 |  | O | cis; mp. 130°C |
| 139 | B4 | ethyl | O | cis; mp. 180°C |
| 188 | B4 | NH ₂ | O | cis + trans |
| 189 | B4 |  | O | cis; mp. 154°C |
| 190 | B4 |  | O | trans; mp. 156°C |
| 191 | B4 |  | O | cis; mp. >260°C |
| 192 | B4 |  | O | .H ₂ O (1:1); trans; mp. 248°C |

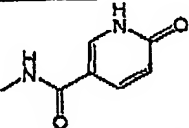
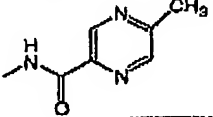
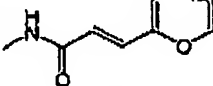
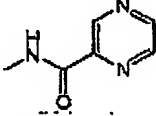
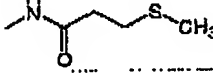
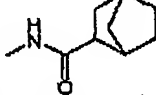
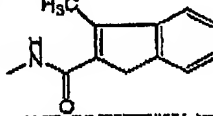
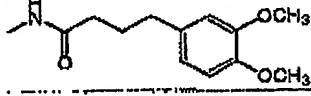
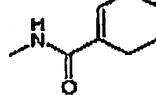
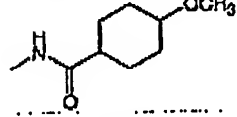
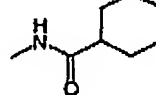
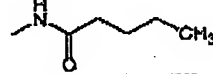
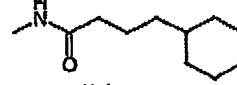
- 79 -

| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|----------------|---|---|
| 193 | B4 | | O | cis; mp. 224°C |
| 194 | B4 | | O | trans; mp. 234°C |
| 195 | B4 | | O | cis; mp. 108°C |
| 196 | B4 | | O | trans; mp. 127°C |
| 197 | B4 | | O | cis; mp. 150°C |
| 198 | B4 | | O | trans; mp. 90°C |
| 199 | B4 | | O | LC/MS [M+H] ⁺ ; 475.4 |
| 200 | B4 | | O | LC/MS [M+H] ⁺ ; 464.3 |
| 201 | B4 | | O | LC/MS [M+H] ⁺ ; 523.3 |
| 202 | B4 | | O | LC/MS [M+H] ⁺ ; 465.3 |
| 203 | B4 | | O | LC/MS [M+H] ⁺ ; 475.4 |
| 204 | B4 | | O | LC/MS [M+H] ⁺ ; 465.3 |
| 205 | B4 | | O | - |
| 319 | B4 | | O | (cis); ethanedioate(1:1); mp.: 160°C |

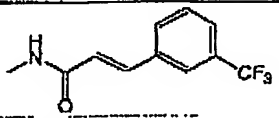
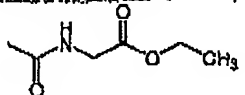
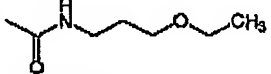
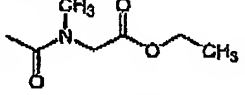
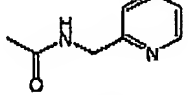
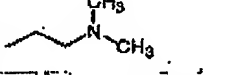
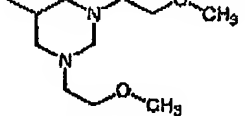

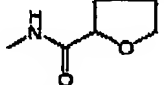
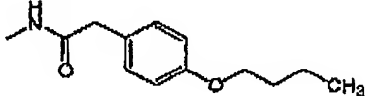
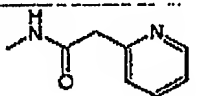
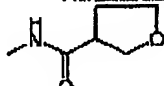
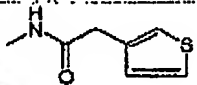
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| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|---|-----------------|----------------------------|
| 320 | B4 |  | O | (cis); mp.:150°C |
| 321 | B4 | methoxy | CH ₂ | (cis);.HCl(1:1); mp.:118°C |
| 322 | B4 | n-butyl | O | (cis);.HCl(1:1); mp.:158°C |
| 323 | B4 |  | O | - |
| 324 | B4 |  | O | - |
| 325 | B4 |  | O | - |
| 326 | B4 |  | O | - |
| 327 | B4 |  | O | - |
| 328 | B4 |  | O | - |
| 329 | B4 |  | O | - |
| 330 | B4 |  | O | - |
| 331 | B4 |  | O | - |
| 332 | B4 |  | O | - |
| 333 | B4 |  | O | - |

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| Co. no. | Ex. no. | R ² | X | physical data |
|---------|---------|---|---|---------------|
| 334 | B4 |  | O | - |
| 335 | B4 |  | O | - |
| 336 | B4 |  | O | - |
| 337 | B4 |  | O | - |
| 338 | B4 |  | O | - |
| 339 | B4 |  | O | - |
| 340 | B4 |  | O | - |
| 341 | B4 |  | O | - |
| 342 | B4 |  | O | - |
| 343 | B4 |  | O | - |
| 344 | B4 |  | O | - |
| 345 | B4 |  | O | - |
| 346 | B4 |  | O | - |

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| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|---|---|--|
| 347 | B4 |  | O | - |
| 348 | B4 | CH ₂ OC(=O)CH ₃ | O | (cis); mp.: 74°C |
| 349 | B4 |  | O | - |
| 350 | B4 |  | O | - |
| 351 | B4 |  | O | - |
| 352 | B4 |  | O | - |
| 353 | B4 |  | O | (A); HCl(1:2).H ₂ O(1:1); mp.: 166°C |
| 354 | B4 |  | O | (cis) |
| 355 | B4 |  | O | - |
| 356 | B4 |  | O | - |
| 357 | B4 |  | O | - |
| 358 | B4 |  | O | - |
| 359 | B4 |  | O | - |
| 360 | B4 |  | O | - |

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| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|----------------|---|---------------|
| 361 | B4 | | O | - |
| 362 | B4 | | O | - |
| 363 | B4 | | O | - |
| 364 | B4 | | O | - |
| 365 | B4 | | O | - |
| 366 | B4 | | O | - |
| 367 | B4 | | O | - |
| 368 | B4 | | O | - |
| 369 | B4 | | O | - |
| 370 | B4 | | O | - |
| 371 | B4 | | O | - |
| 372 | B4 | | O | - |

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| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|----------------|---|---------------------|
| 373 | B4 | | O | - |
| 374 | B4 | | O | - |
| 375 | B4 | | O | - |
| 376 | B4 | | O | - |
| 377 | B4 | | O | - |
| 378 | B4 | | O | - |
| 379 | B4 | | O | - |
| 380 | B4 | | O | - |
| 381 | B4 | | O | - |
| 382 | B4 | | O | - |
| 383 | B4 | | O | (cis); mp.: 148°C |
| 384 | B4 | | O | (trans); mp.: 141°C |

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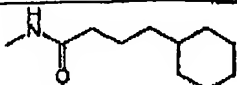
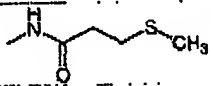
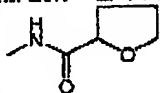
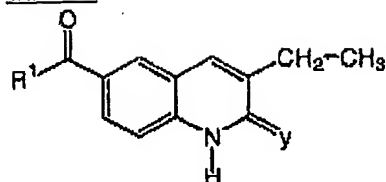
| Co. no. | Ex. no. | R ² | X | physical data |
|------------|------------|---|---|--------------------|
| 385 | B4 |  | O | mp.:130°C |
| 386 | B4 |  | O | (cis); mp.:140°C |
| 387 | B4 |  | O | (trans); mp.:155°C |

Table 3



| Co. no. | Ex. no. | Y. | R¹ | physical data |
|---------|---------|----|-----------------------------|----------------------|
| 140 | B4 | O | | mp. 220°C |
| 141 | B4 | O | | mp. 213°C |
| 142 | B4 | O | | mp. 148°C |
| 143 | B4 | O | 1-methylcyclohexyl | mp. 195-210°C |
| 144 | B4 | O | 3-methoxycyclohexyl | cis; mp. 156°C |
| 145 | B4 | O | 3-methoxycyclohexyl | trans; mp. 156-163°C |
| 146 | B4 | O | 4-(dimethylethyl)cyclohexyl | mp. 230°C |
| 147 | B4 | O | 4-(methylethoxy)cyclohexyl | mp. 186°C |
| 148 | B4 | O | 4-methylcyclohexyl | trans; mp. 214°C |
| 36 | B4 | S | 4-methoxycyclohexyl | cis; mp. 224°C |
| 37 | B4 | S | 4-methoxycyclohexyl | trans; mp. 220°C |
| 149 | B4 | O | | mp. 188°C |
| 40 | B4 | O | | mp. 192°C |
| 150 | B4 | O | | cis; mp. 226°C |
| 151 | B4 | O | | trans; mp. 226°C |
| 152 | B4 | O | | mp. 213°C |
| 153 | B4 | O | | mp. 200°C |

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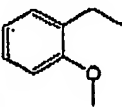
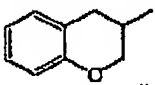
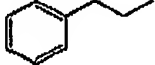
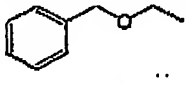
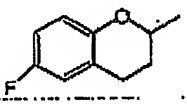
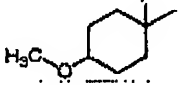
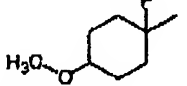
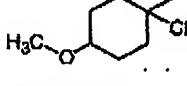



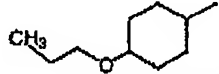
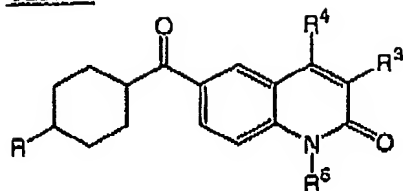
| Co. no. | Ex. no. | Y. | R ¹ | physical data |
|------------|------------|----|---|------------------|
| 154 | B4 | O |  | mp. 210°C |
| 155 | B4 | O | 4,4-dimethylcyclohexyl | mp. 242°C |
| 388 | B4 | O | CH ₂ CH(CH ₃) ₂ | mp. 189°C |
| 389 | B4 | O |  | mp. 228°C |
| 390 | B4 | O |  | mp. 197°C |
| 391 | B4 | O |  | mp. 145°C |
| 392 | B4 | O |  | mp. 192°C |
| 393 | B4 | O |  | (B); mp.:224°C |
| 394 | B4 | O |  | (A); mp.:201°C |
| 395 | B4 | O |  | (A); mp.:207°C |
| 396 | B4 | O |  | mp.:212°C |
| 397 | B4 | O |  | (B); mp.:238°C |
| 398 | B4 | O |  | mp.:234°C |
| 399 | B4 | O |  | (cis); mp.:192°C |

Table 4



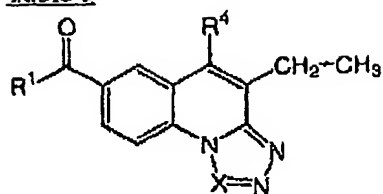
| Co. no. | Ex. o. | t ³ | R ⁴ | t ⁵ | R | physical data |
|---------|--------|----------------|----------------|---|------------------|----------------------------------|
| 156 | B4 | ethyl | H | H | OCH ₃ | trans; mp. 252°C |
| 157 | B4 | H | H | H | OCH ₃ | (cis + trans); mp. 244°C |
| 158 | B4 | H | methyl | H | OCH ₃ | cis; mp. >260°C |
| 159 | B4 | methyl | H | H | OCH ₃ | cis; mp. 254°C |
| 160 | B4 | methyl | H | H | OCH ₃ | trans; mp. >260°C |
| 161 | B4 | propyl | H | H | OCH ₃ | mp. 208°C |
| 162 | B4 | propyl | H | H | OCH ₃ | trans; mp. 232°C |
| 9 | B4 | ethyl | H | H | OCH ₃ | cis; mp. 224-226°C |
| 43 | B5 | ethyl | H | CH ₃ | OCH ₃ | trans; mp. 116°C |
| 42 | B5 | ethyl | H | CH ₃ | OCH ₃ | cis; mp. 125°C |
| 44 | B6 | ethyl | H | CH ₂ -COOC ₂ H ₅ | OCH ₃ | cis; mp. 152°C |
| 45 | B4 | ethyl | H | CH ₂ -COOC ₂ H ₅ | OCH ₃ | trans; mp. 147°C |
| 46 | B4 | ethyl | H | benzyl | OCH ₃ | cis; mp. 137°C |
| 47 | B4 | ethyl | H | benzyl | OCH ₃ | trans; mp. 130°C |
| 50 | B7 | methyl | H | H | H | mp. 256.1°C |
| 163 | B4 | ethyl | ethyl | H | OCH ₃ | cis; mp. 221°C |
| 164 | B4 | ethyl | ethyl | H | OCH ₃ | cis; mp. 221°C |
| 165 | B4 | ethyl | ethyl | H | OCH ₃ | trans; mp. 215°C |
| 166 | B4 | ethyl | H | | OCH ₃ | LC/MS [M+H] ⁺ ; 429.4 |
| 167 | B4 | ethyl | H | | OCH ₃ | LC/MS [M+H] ⁺ ; 451.3 |
| 168 | B4 | H | H | H | OCH ₃ | cis; mp. 106°C |
| 169 | B4 | ethyl | H | | OCH ₃ | LC/MS [M+H] ⁺ ; 409.3 |

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| Co. no. | Ex. o. | R^3 | R^4 | R^5 | R | physical data |
|------------|-----------|----------------------------------|--------------|--------------|------------------|---------------|
| 400 | B9 | ethyl | H | | OCH ₃ | - |
| 401 | B9 | ethyl | H | | OCH ₃ | - |
| 402 | B9 | ethyl | H | | OCH ₃ | - |
| 403 | B9 | ethyl | H | | OCH ₃ | - |
| 404 | B9 | ethyl | H | | OCH ₃ | - |
| 405 | B9 | ethyl | H | | OCH ₃ | - |
| 406 | B4 | ethyl | H | | OCH ₃ | - |
| 407 | B4 | ethyl | H | | OCH ₃ | - |
| 408 | B4 | ethyl | H | | OCH ₃ | - |
| 409 | B3b | | H | H | OCH ₃ | mp.: 168°C |
| 410 | B4 | CH ₂ OCH ₃ | H | H | OCH ₃ | mp.: 194°C |
| 508 | B4 | ethyl | H | | OCH ₃ | - |
| 520 | B9 | ethyl | H | | OCH ₃ | - |

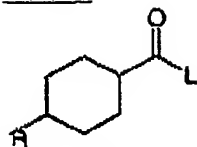
- 90 -

Table 5

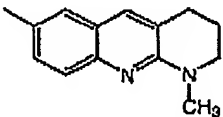
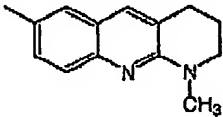
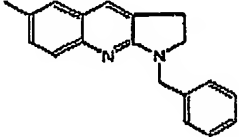
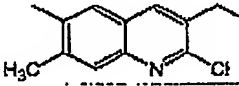
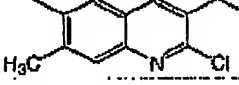
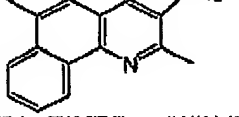
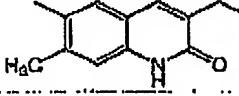
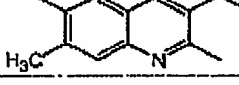
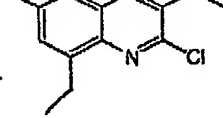
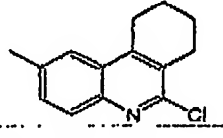
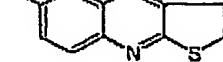


| Co. no. | Ex. no. | R ⁴ | R ¹ | X | physical data |
|---------|---------|----------------|-------------------|----|----------------------|
| 33 | B4 | H | methoxycyclohexyl | CH | cis; mp. 224°C |
| 34 | B4 | H | methoxycyclohexyl | CH | trans; mp. 185°C |
| 35 | B4 | H | methoxycyclohexyl | N | cis; mp. 160-172°C |
| 170 | B4 | H | methoxycyclohexyl | N | trans; mp. 146°C |
| 171 | B4 | H | | N | (B); mp. 165°C |
| 172 | B4 | H | methylcyclohexyl | N | cis+trans; mp. 143°C |
| 173 | B4 | ethyl | methoxycyclohexyl | N | cis; mp. 126°C |
| 411 | B4 | H | | N | mp. 109°C |
| 412 | B4 | H | | N | mp. 180°C |
| 413 | B4 | H | | N | (A) |
| 414 | B4 | H | | N | mp. 156°C |

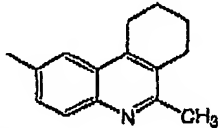
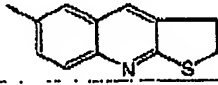
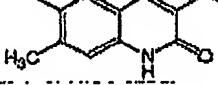
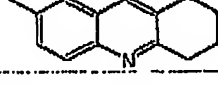
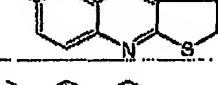
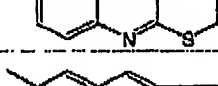
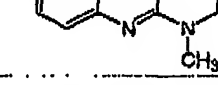
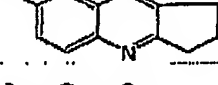
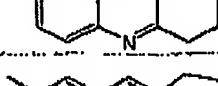
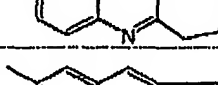
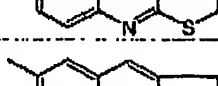
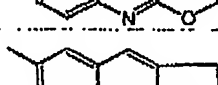

Table 6



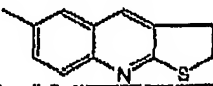
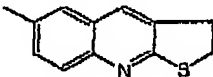
| Co. no. | Ex. no. | R | L | physical data |
|---------|---------|------------------|---|------------------|
| 49 | B7 | H | | - |
| 174 | B3b | OCH ₃ | | cis; mp. 115°C |
| 175 | B3b | OCH ₃ | | trans; mp. 141°C |
| 176 | B3b | OCH ₃ | | cis; mp. 149°C |
| 177 | B3b | OCH ₃ | | mp. 126°C |
| 178 | B3b | OCH ₃ | | trans; mp. 160°C |
| 179 | B3b | OCH ₃ | | cis; mp. 119°C |
| 180 | B3b | OCH ₃ | | trans; mp. 124°C |
| 181 | B3b | OCH ₃ | | trans; mp. 92°C |
| 206 | B3b | OCH ₃ | | cis; m.p. 144°C |

| Co. no. | Ex. no. | R | L | physical data |
|------------|------------|------------------|---|-------------------|
| 207 | B3b | OCH ₃ |  | trans; m.p. 125°C |
| 208 | B3b | OCH ₃ |  | cis; m.p. 127°C |
| 209 | B3b | OCH ₃ |  | cis; m.p. 101°C |
| 210 | B3b | OCH ₃ |  | cis; m.p. 104°C |
| 211 | B3b | OCH ₃ |  | trans; m.p. 134°C |
| 212 | B4 | OCH ₃ |  | cis; m.p. 141°C |
| 213 | B4 | OCH ₃ |  | trans; m.p. 215°C |
| 214 | B4 | OCH ₃ |  | cis; m.p. 139°C |
| 215 | B3b | OCH ₃ |  | trans |
| 415 | B3b | OCH ₃ |  | (cis); mp.:136°C |
| 416 | B3b | OCH ₃ |  | (cis) |

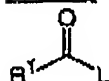
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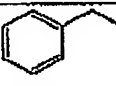
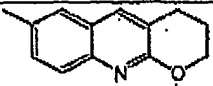
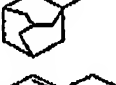
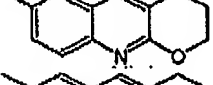
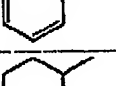
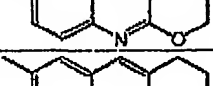

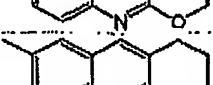

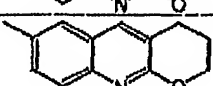
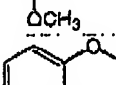
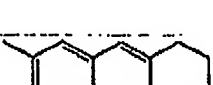
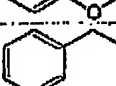
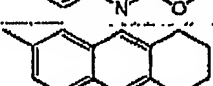
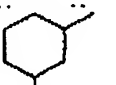
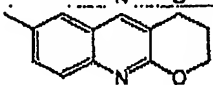
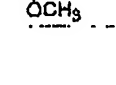
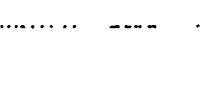
| Co. no. | Ex. no. | R | L | physical data |
|------------|------------|------------------|---|-------------------------------|
| 417 | B4 | OCH ₃ |  | (cis); mp.:149°C |
| 418 | B3b | OCH ₃ |  | (trans); mp.:132°C |
| 419 | B4 | OCH ₃ |  | (cis); mp.:217°C |
| 420 | B3b | OCH ₃ |  | (cis); HCl(1:1); mp.:200°C |
| 421 | B4 | OH |  | (cis); mp.:215°C |
| 422 | B4 | OH |  | (trans); mp.:178°C |
| 423 | B3b | OCH ₃ |  | mp.:160°C |
| 424 | B3b | OCH ₃ |  | (cis); mp.:106°C |
| 425 | B3b | OCH ₃ |  | (trans); mp.:120°C |
| 426 | B3b | OCH ₃ |  | (cis); mp.:121°C |
| 427 | B3b | H |  | mp.:156°C |
| 428 | B3b | OCH ₃ |  | (cis); mp.:156°C |
| 429 | B3b | OCH ₃ |  | (trans); mp.:197°C |

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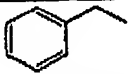
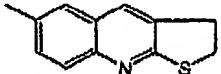
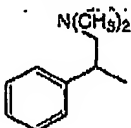
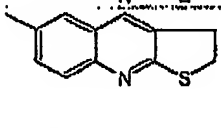
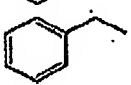
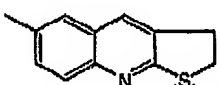
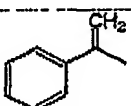
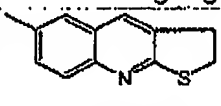

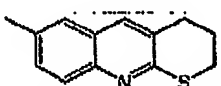
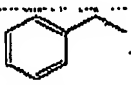
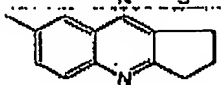
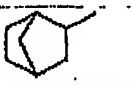
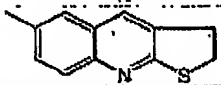
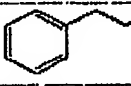
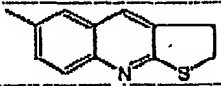
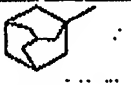
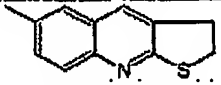
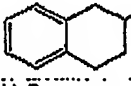
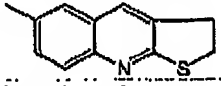
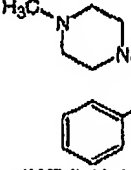
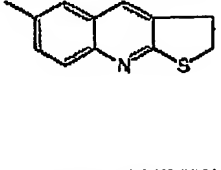
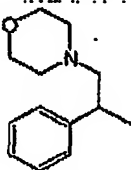
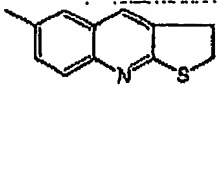
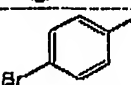
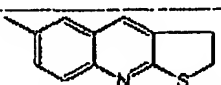
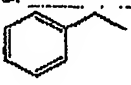
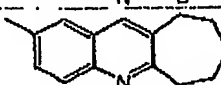
| Co. no. | Ex. no. | R | L | physical data |
|------------|------------|-----------------|---|---------------|
| 430 | B3b | CH ₃ |  | (B) |
| 431 | B3b | CH ₃ |  | (A) |

5 Table 7

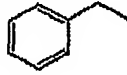
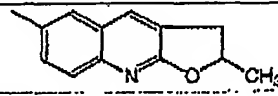
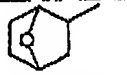
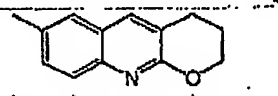

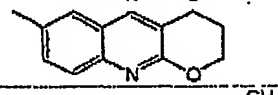

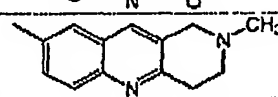
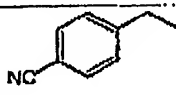
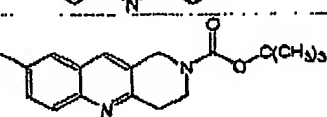
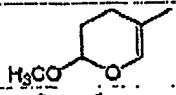
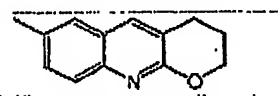

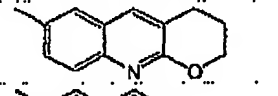
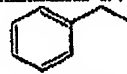
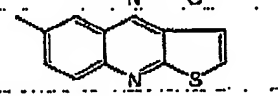
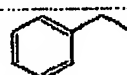
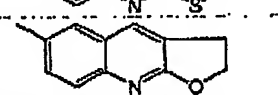

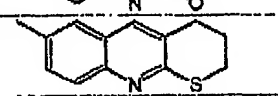

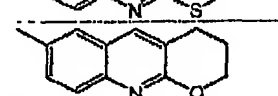
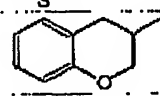
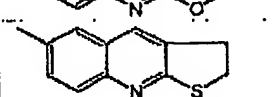
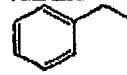
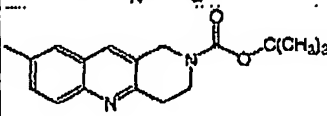
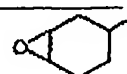
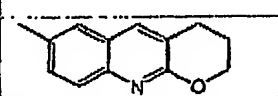
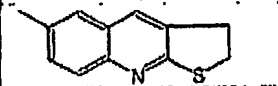


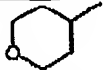
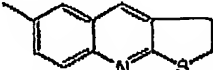
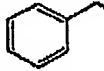
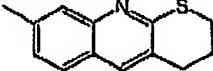
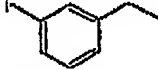
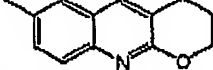
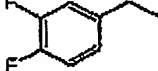
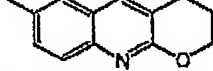
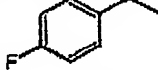
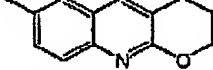
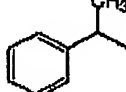
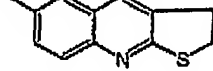
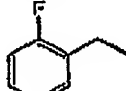
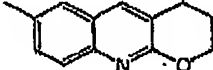
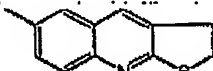
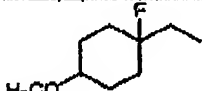
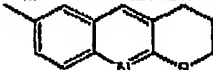
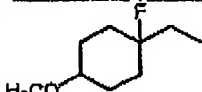
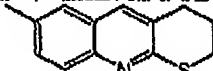
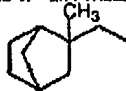
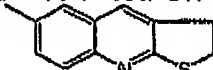
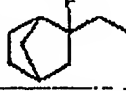
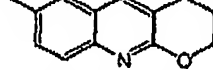
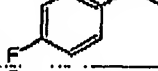
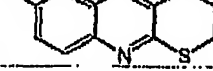
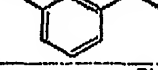
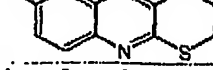
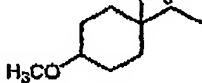
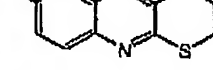
| Co. no. | Ex. no. | R ¹ | L | physical data |
|------------|------------|---|--|-----------------------|
| 432 | B16 |  |  | mp.:128°C |
| 433 | B4 |  |  | mp.:175°C |
| 434 | B4 |  |  | mp.:170°C |
| 435 | B4 |  |  | mp.:103°C |
| 436 | B4 |  |  | mp.:151°C |
| 437 | B4 |  |  | (trans); mp.:110°C |
| 438 | B4 |  |  | mp.:150°C |
| 439 | B4 |  |  | mp.:150°C |
| 440 | B4 |  |  | (cis) |

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| Co. no. | Ex. no. | R ¹ | L | physical data |
|------------|------------|---|--|---------------|
| 441 | B4 |  |  | mp.:166°C |
| 442 | B4 |  |  | mp.:173°C |
| 443 | B4 |  |  | mp.:208°C |
| 444 | B4 |  |  | mp.:149°C |
| 445 | B4 |  |  | mp.:133°C |
| 446 | B3b |  |  | mp.:150°C |
| 447 | B3b |  |  | mp.:165°C |
| 448 | B3b |  |  | mp.:147°C |
| 449 | B3b |  |  | mp.:154°C |
| 450 | B3b |  |  | mp.:157°C |
| 451 | B4 |  |  | mp.:190°C |
| 452 | B4 |  |  | mp.:187°C |
| 453 | B3b |  |  | mp.:200°C |
| 454 | B3b |  |  | mp.:160°C |

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| Co. no. | Ex. no. | R ¹ | L | physical data |
|------------|------------|---|--|-----------------------------|
| 455 | B3b |  |  | mp.:139°C |
| 456 | B3b |  |  | (A); mp.:174°C |
| 457 | B3b |  |  | (B); mp.:160°C |
| 458 | B3b |  |  | mp.:184°C |
| 459 | B4 |  |  | - |
| 460 | B4 |  |  | mp.:134°C |
| 461 | B4 |  |  | (B); mp.:156°C |
| 462 | B4 |  |  | mp.:153°C |
| 463 | B3b |  |  | mp.:161°C |
| 464 | B4 |  |  | mp.:135°C |
| 465 | B4 |  |  | mp.:131°C |
| 466 | B3b |  |  | .HCl(1:1); mp.:206°C |
| 467 | B3d |  |  | mp.:142°C |
| 468 | B4 |  |  | .hydrate(1:1); mp.:104°C |
| 469 | B3b | dimethylethyl |  | mp.:104°C |

| Co. no. | Ex. no. | R ¹ | L | physical data |
|------------|------------|---|--|----------------|
| 470 | B3b |  |  | mp.:161°C |
| 472 | B3b |  |  | mp.:144°C |
| 473 | B4 |  |  | mp.:143°C |
| 474 | B4 |  |  | mp.:196°C |
| 475 | B4 |  |  | mp.:162°C |
| 476 | B4 |  |  | mp.:171°C |
| 477 | B4 |  |  | mp.:155°C |
| 478 | B2 | trimethylmethyl |  | mp.:124°C |
| 479 | B4 |  |  | (A); mp.:146°C |
| 480 | B4 |  |  | (B); mp.:162°C |
| 481 | B4 |  |  | (A); mp.:129°C |
| 482 | B4 |  |  | mp.:115°C |
| 483 | B2 |  |  | mp.:187°C |
| 484 | B2 |  |  | mp.:162°C |
| 485 | B4 |  |  | (A); mp.:130°C |

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| Co. no. | Ex. no. | R ¹ | L | physical data |
|------------|------------|----------------|---|----------------|
| 486 | B4 | | | (A); mp.:124°C |
| 487 | B4 | | | (B); mp.:128°C |
| 488 | B4 | | | mp.:85°C |
| 489 | B2 | | | mp.:150°C |
| 490 | B4 | | | (A); mp.:117°C |
| 491 | B2 | | | mp.:220°C |
| 492 | B4 | | | mp.:136°C |
| 493 | B2 | | | mp.:131°C |
| 494 | B4 | | | (A); mp.:125°C |
| 495 | B4 | | | mp.:135°C |
| 496 | B4 | | | mp.:139°C |
| 497 | B4 | | | mp.:127°C |
| 498 | B16 | | | mp.:195°C |
| 499 | B2 | | | mp.:201°C |

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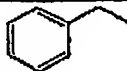
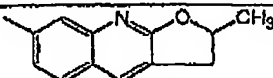
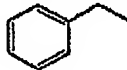
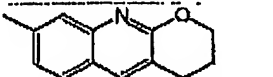
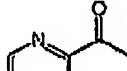
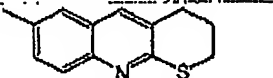



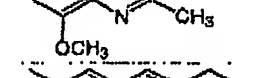

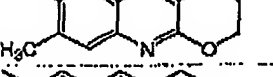

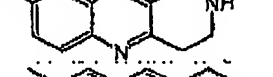
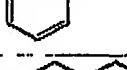
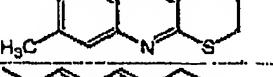

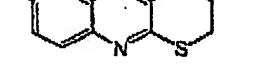
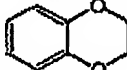
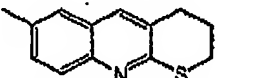
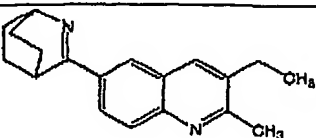
| Co. no. | Ex. no. | R ¹ | L | physical data |
|---------|---------|---|--|---------------|
| 500 | B3b |  |  | mp.:143°C |
| 501 | B3b |  |  | mp.:137°C |
| 502 | B2 |  |  | mp.:210°C |
| 503 | B3d |  |  | mp.:134°C |
| 504 | B2 |  |  | mp.:163°C |
| 505 | B4 |  |  | mp.:142°C |
| 506 | B2 |  |  | mp.:139°C |
| 507 | B4 |  |  | mp.:171°C |
| 512 | B3b |  |  | - |
| 523 | B3b |  |  | - |

Table 8:

| Co. no. | Ex. no. | Structure | physical data |
|---------|---------|---|---------------|
| 511 | B11 |  | - |

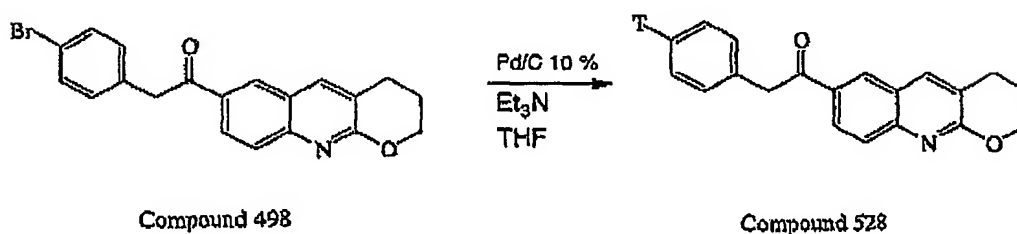
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| Co. no. | Ex. no. | Structure | physical data |
|---------|---------|-----------|---------------|
| 514 | B12 | | - |
| 515 | B13 | | - |
| 524 | B9a | | mp.: 185°C |
| 471 | B15 | | (E) |
| 526 | B14 | | .HCl(1:1) |

C. Preparation of radioactively labelled compounds

C.1 [^3H]-labelled compounds

5



- 10 To a carefully measured amount of palladium on carbon (10 %, 0.872 mg) was added a solution of compound 498 (I, 0.919 mg, 2.4 μmol) and triethylamine (0.92 μl , 6.6 μmol) in sodium-dried tetrahydrofuran (175 μl). The reaction flask was connected to a tritiation manifold system and the reaction mixture was carefully degassed. Tritium gas (19.5 Ci at a pressure of 1017 mbar) was generated from uranium tritide and was

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allowed onto the at room temperature stirred reaction mixture. After 30 min, the reaction mixture was frozen with liquid nitrogen and the excess of tritium gas was recaptured onto uranium sponge. The solvent was lyophilized from the reaction mixture. Methanol (100 μ l) was introduced and lyophilized in order to remove labile tritium. This procedure was repeated twice more. The residue was taken up in ethanol, filtered over a GHP Acrodisk 13 mm syringe filter and depleted with ethanol to a total volume of 50.0 ml. It contained 71 mCi of radioactivity with [3 H]-compound 528 (II) at a 67 % radiochemical purity. From this amount, a fraction (5.0 ml) was taken and thoroughly purified in portions via preparative HPLC (Kromasil KR 100-10, column dimensions 4.6 mm ID x 300 mm). UV detection took place at 265 nm. Elution was performed isocratically with water-methanol-acetonitrile-diisopropylamine (47:26.5:26.5:0.2; v/v/v/v) at a flow rate of 2.0 ml/min. The product containing fractions were combined and concentrated under vacuum at 30°C. The residue was dissolved in ethanol (5.0 ml) and concentrated again. This procedure was repeated twice more. The remaining residue was finally dissolved in ethanol (20.0 ml) and stored as such. The batch contained [3 H]-compound 528 (II) with a total radioactivity of 3.83 mCi at a purity > 98 % and at a specific activity of about 25 Ci/mmol.

20 D. Pharmacological examples

D1. Signal transduction at the cloned rat mGluR1 receptor in CHO cells

CHO cells expressing the mGluR1 receptor were plated in precoated black 96-well plates. The next day, the effect of the present compounds on glutamate-activated intracellular Ca^{2+} increase was evaluated in a fluorescent based assay. The cells were loaded with Fluo-3 AM, plates were incubated for 1 hour at room temperature in the dark, cells were washed and the present compounds were added onto the cells for 20 minutes. After this incubation time, the glutamate-induced Ca^{2+} rise was recorded for each well in function of time using the Fluorescent Image Plate Reader (FLIPR, Molecular Devices Inc.). Relative fluorescence units were recorded and average data graphs of quadruple wells were obtained. Concentration-response curves were constructed based on peak fluorescence (maximum signal between 1 and 90 secondes) for each concentration of tested compound. pIC_{50} values are the $-\log$ values of the concentration of the tested compounds resulting in 50% inhibition of the glutamate-induced intracellular Ca^{2+} rise.

The compounds according to the present invention exhibited a pIC_{50} value of at least 5.

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The compounds that are included in the Tables 1-8 exhibited a pIC_{50} value of at least 6.

A particular group of compounds exhibited a pIC_{50} value between 7 and 8. It concerns the compounds listed in Table 9.

Table 9:

| Com.nr. | pIC_{50} |
|---------|------------|
| 463 | 7.98 |
| 441 | 7.95 |
| 334 | 7.95 |
| 22 | 7.94 |
| 421 | 7.94 |
| 15 | 7.93 |
| 440 | 7.93 |
| 139 | 7.93 |
| 178 | 7.92 |
| 338 | 7.91 |
| 87 | 7.90 |
| 462 | 7.90 |
| 394 | 7.90 |
| 423 | 7.89 |
| 21 | 7.87 |
| 220 | 7.87 |
| 479 | 7.86 |
| 483 | 7.86 |
| 485 | 7.84 |
| 9 | 7.84 |
| 110 | 7.84 |
| 248 | 7.84 |
| 341 | 7.83 |
| 163 | 7.81 |
| 433 | 7.79 |
| 238 | 7.79 |
| 224 | 7.78 |
| 437 | 7.78 |
| 498 | 7.78 |
| 449 | 7.77 |

| Com.nr. | pIC_{50} |
|---------|------------|
| 281 | 7.63 |
| 487 | 7.63 |
| 299 | 7.63 |
| 431 | 7.61 |
| 98 | 7.57 |
| 464 | 7.57 |
| 446 | 7.56 |
| 251 | 7.55 |
| 484 | 7.54 |
| 494 | 7.53 |
| 128 | 7.52 |
| 344 | 7.52 |
| 161 | 7.49 |
| 298 | 7.48 |
| 454 | 7.45 |
| 456 | 7.45 |
| 277 | 7.44 |
| 91 | 7.43 |
| 356 | 7.42 |
| 229 | 7.41 |
| 333 | 7.41 |
| 326 | 7.41 |
| 369 | 7.40 |
| 430 | 7.39 |
| 435 | 7.38 |
| 35 | 7.36 |
| 228 | 7.36 |
| 429 | 7.36 |
| 117 | 7.35 |
| 291 | 7.35 |

| Com.nr. | pIC_{50} |
|---------|------------|
| 89 | 7.25 |
| 108 | 7.25 |
| 373 | 7.25 |
| 255 | 7.23 |
| 527 | 7.23 |
| 303 | 7.22 |
| 296 | 7.22 |
| 221 | 7.21 |
| 193 | 7.21 |
| 14 | 7.20 |
| 131 | 7.19 |
| 438 | 7.19 |
| 148 | 7.18 |
| 496 | 7.18 |
| 236 | 7.17 |
| 332 | 7.17 |
| 481 | 7.16 |
| 191 | 7.16 |
| 457 | 7.14 |
| 20 | 7.14 |
| 145 | 7.13 |
| 268 | 7.13 |
| 512 | 7.13 |
| 474 | 7.13 |
| 10 | 7.11 |
| 307 | 7.11 |
| 426 | 7.11 |
| 466 | 7.10 |
| 97 | 7.08 |
| 83 | 7.08 |

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| Com.nr. | pIC ₅₀ |
|---------|-------------------|
| 242 | 7.76 |
| 346 | 7.74 |
| 182 | 7.73 |
| 486 | 7.73 |
| 447 | 7.72 |
| 7 | 7.72 |
| 175 | 7.71 |
| 475 | 7.71 |
| 480 | 7.71 |
| 213 | 7.70 |
| 239 | 7.70 |
| 241 | 7.67 |
| 461 | 7.65 |
| 115 | 7.64 |
| 445 | 7.63 |

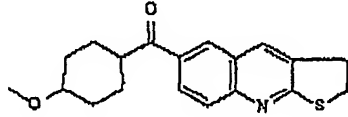
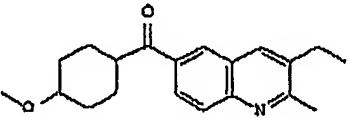
| Com.nr. | pIC ₅₀ |
|---------|-------------------|
| 313 | 7.35 |
| 280 | 7.34 |
| 460 | 7.34 |
| 482 | 7.34 |
| 343 | 7.33 |
| 425 | 7.32 |
| 473 | 7.32 |
| 287 | 7.31 |
| 448 | 7.31 |
| 243 | 7.29 |
| 323 | 7.28 |
| 159 | 7.28 |
| 289 | 7.27 |
| 184 | 7.26 |
| 436 | 7.26 |

| Com.nr. | pIC ₅₀ |
|---------|-------------------|
| 434 | 7.08 |
| 300 | 7.08 |
| 199 | 7.07 |
| 290 | 7.06 |
| 112 | 7.05 |
| 348 | 7.05 |
| 286 | 7.03 |
| 442 | 7.03 |
| 422 | 7.02 |
| 283 | 7.02 |
| 318 | 7.02 |
| 36 | 7.00 |
| 396 | 7.00 |

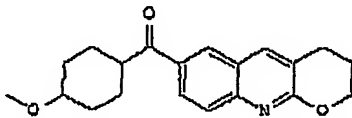
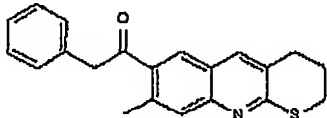
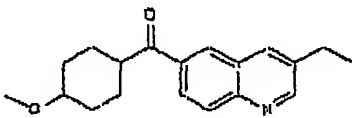
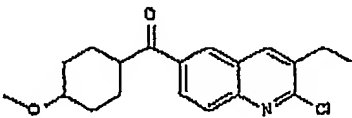
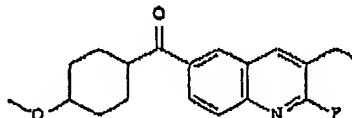
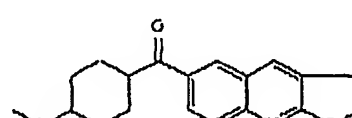
A particular group of compounds exhibited a pIC₅₀ value of at least 8. It concern the compounds listed in Table 10.

Table 10 :

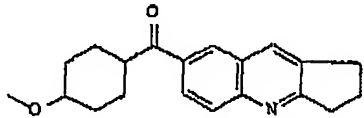
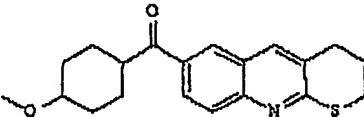
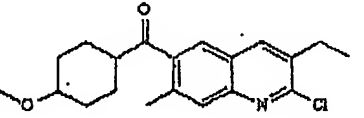
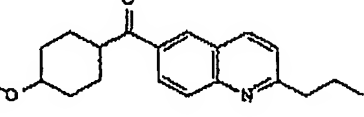
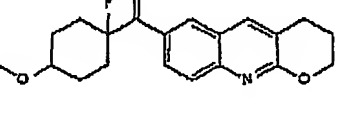
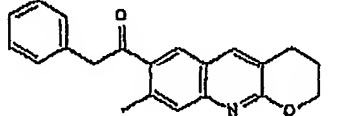
5

| Comp. nr. | Structure | pIC ₅₀ |
|-----------|--|-------------------|
| 416 |  <p>(CIS)</p> | 8.587 |
| 27 |  <p>(CIS)</p> | 8.527 |

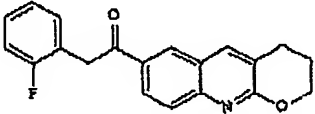
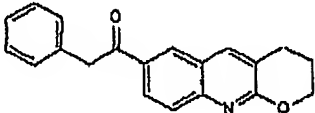
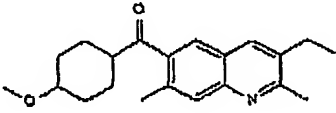
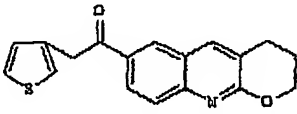
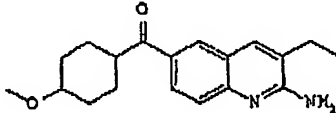
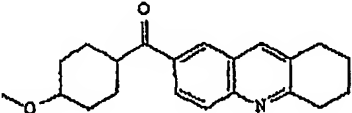
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| Comp. nr. | Structure | pIC50 |
|--------------|--|-------|
| 174 |  (CIS) | 8.49 |
| 506 |  | 8.48 |
| 25 |  (CIS) | 8.45 |
| 4 |  (CIS) | 8.4 |
| 19 |  (CIS) | 8.38 |
| 429 |  (CIS) | 8.38 |

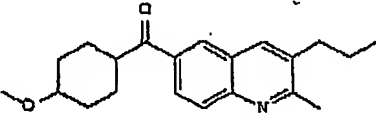
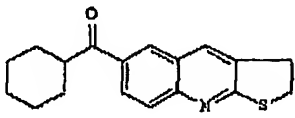
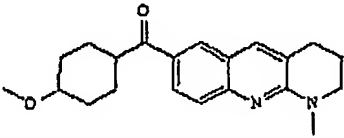
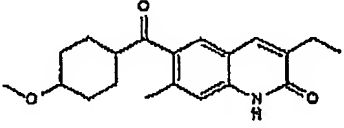
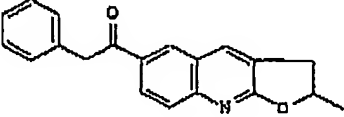
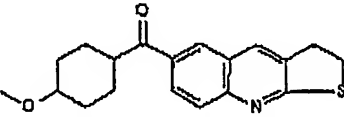
- 105 -

| Comp. nr. | Structure | pIC50 |
|--------------|--|-------|
| 424 |  (CIS) | 8.355 |
| 176 |  (CIS) | 8.33 |
| 210 |  (CIS) | 8.315 |
| 114 |  (CIS) | 8.28 |
| 488 |  (CIS) | 8.27 |
| 504 |  (CIS) | 8.27 |

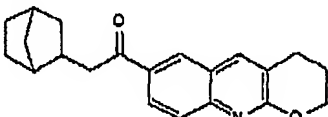
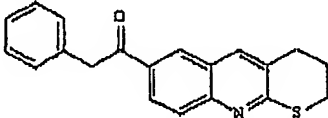
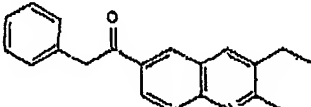
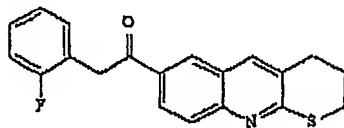
- 106 -

| Comp. nr. | Structure | pIC50 |
|--------------|--|-------|
| 477 |  | 8.25 |
| 432 |  | 8.237 |
| 214 |  (CIS) | 8.233 |
| 465 |  | 8.145 |
| 135 |  (CIS) | 8.14 |
| 420 |  (CIS) Hydrochloride (1:1) | 8.135 |

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| Comp. nr. | Structure | pIC50 |
|--------------|--|-------|
| 292 |  (CIS) | 8.13 |
| 427 |  | 8.115 |
| 208 |  (CIS) | 8.095 |
| 419 |  (CIS) | 8.065 |
| 455 |  | 8.055 |
| 418 |  (TRANS) | 8.045 |

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| Comp. nr. | Structure | pIC50 |
|--------------|---|-------|
| 497 |  | 8.025 |
| 439 |  | 8.023 |
| 237 |  | 8.01 |
| 499 |  | 8 |

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D2. In vitro binding experiments with a [^3H]-radiolabelled compound according to the invention

As [^3H]-radiolabelled compound is used : compound 528, hereafter named as
5 [^3H]Compound A, which is the radiolabelled equivalent of compound 432.

Cell membrane fractions, prepared from either CHO-cells transfected with the rat mGlu1a receptor and L929sA-cells transfected with the human mGlu1a receptor according to Mintel et al., J. Neurochem. 75, 2590-2601, 2000 - were incubated for 1
10 hour at room temperature in 6 different membrane protein concentrations (0, 20, 50, 80, 100, 150 μg protein/assay) with a radioactive [^3H]-labelled substance (described hereinafter as the [^3H]-ligand). This [^3H]-ligand is known to bind specifically to the mGlu1 receptor, thus labeling this receptor. The [^3H]-ligand used is mentioned in Table 11. After the incubation, the labelled membranes were harvested on GF/C glass
15 fibre filters and rinsed three times with 3 ml of a cold buffer solution to remove non-bound [^3H]-ligands. Subsequently the glass fibre filters, with the harvested membranes, were placed in plastic mini-vials and 3.0 ml of Ultima GoldTM scintillation cocktail was added. After overnight incubation, the vials were vigorously shaken and the radioactivity was counted in a Packard Tri-Carb 1500 CA liquid
20 scintillation analyzer. Said radioactivity is proportional to the membrane labelling by the [^3H]-ligand. Specific membrane labelling by the [^3H]-ligand was distinguished from the non-specific membrane labelling by selectively inhibiting the labelling of the receptor site by another substance (unlabelled) known to compete with the [^3H]-ligand for binding to said receptor site. As competing substance, compound 135 was used for
25 the [^3H]Compound A ligand and glutamate for the [^3H]-Quisqualate ligand. The non-specific binding is expressed as the ratio of the total binding over the binding in the presence of the competing substance in percentage and should be as small as possible.

From Table 11, it can be seen that the non-specific binding is excellent for the
30 compound according to the invention.

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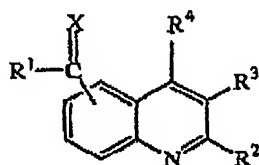
Table 11 : Non Specific Binding (NSB) for different mGluR1 ligands for different concentrations.

| $\mu\text{g}/\text{assay}$ | 20 | 50 | 80 | 100 | 150 |
|-----------------------------|----|----|----|-----|-----|
| rat-mGlu1a receptor | | | | | |
| $[^3\text{H}]$ -Quisqualate | 39 | 18 | 9 | 11 | 9 |
| $[^3\text{H}]$ Compound A | 7 | 3 | 3 | 3 | 2 |
| human-mGlu1a receptor | | | | | |
| $[^3\text{H}]$ -Quisqualate | 75 | 40 | 43 | 49 | 34 |
| $[^3\text{H}]$ Compound A | 72 | 53 | 46 | 46 | 38 |

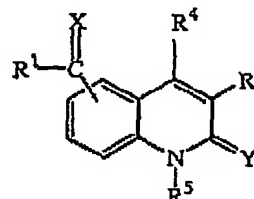
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CLAIMS

1. A radiolabelled compound according to Formula (I-A)* or (I-B)*



(I-A)*

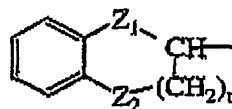


(I-B)*

an *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

X represents O; C(R⁶)₂ with R⁶ being hydrogen, aryl or C₁₋₆alkyl optionally substituted with amino or mono- or di(C₁₋₆alkyl)amino; S or N-R⁷ with R⁷ being amino or hydroxy;

R¹ represents C₁₋₆alkyl; aryl; thienyl; quinoliny; cycloC₃₋₁₂alkyl or (cycloC₃₋₁₂alkyl)C₁₋₆alkyl, wherein the cycloC₃₋₁₂alkyl moiety optionally may contain a double bond and wherein one carbon atom in the cycloC₃₋₁₂alkyl moiety may be replaced by an oxygen atom or an NR⁸-moiety with R⁸ being hydrogen, benzyl or C₁₋₆alkyloxycarbonyl; wherein one or more hydrogen atoms in a C₁₋₆alkyl-moiety or in a cycloC₃₋₁₂alkyl-moiety optionally may be replaced by C₁₋₆alkyl, hydroxyC₁₋₆alkyl, haloC₁₋₆alkyl, aminoC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, arylC₁₋₆alkyloxy, halo, C₁₋₆alkyloxycarbonyl, aryl, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonylamino, halo, piperazinyl, pyridinyl, morpholinyl, thienyl or a bivalent radical of formula -O-, -O-CH₂-O or -O-CH₂-CH₂-O-; or a radical of formula (a-1)



a-1

wherein Z₁ is a single covalent bond, O, NH or CH₂;
Z₂ is a single covalent bond, O, NH or CH₂;
n is an integer of 0, 1, 2 or 3;

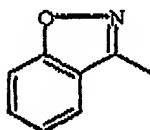
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and wherein each hydrogen atom in the phenyl ring independently
may optionally be replaced by halo, hydroxy, C₁₋₆alkyl,
C₁₋₆alkyloxy or hydroxyC₁₋₆alkyl;

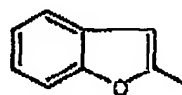
or X and R¹ may be taken together with the carbon atom to which X and R¹ are attached
to form a radical of formula (b-1), (b-2) or (b-3);



b-1



b-2



b-3

R² represents hydrogen; halo; cyano; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylthio;
C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylcarbonyloxyC₁₋₆alkyl;
C₂₋₆alkenyl; hydroxyC₂₋₆alkenyl; C₂₋₆alkynyl; hydroxyC₂₋₆alkynyl; tri(C₁₋₆
alkyl)silaneC₂₋₆alkynyl; amino; mono- or di(C₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxyC₁₋₆alkyl)amino; mono- or di(C₁₋₆alkylthioC₁₋₆alkyl)amino; aryl;
arylC₁₋₆alkyl; arylC₂₋₆alkynyl; C₁₋₆alkyloxyC₁₋₆alkylaminoC₁₋₆alkyl;
aminocarbonyl optionally substituted with C₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl,
C₁₋₆alkyloxycarbonylC₁₋₆alkyl or pyridinylC₁₋₆alkyl;
a heterocycle selected from thienyl, furanyl, pyrrolyl, thiazolyl, oxazolyl,
imidazolyl, isothiazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrazinyl, pyridazinyl,
pyrimidinyl, piperidinyl and piperazinyl, optionally N-substituted with
C₁₋₆alkyloxyC₁₋₆alkyl, morpholinyl, thiomorpholinyl, dioxanyl or dithianyl ;
a radical -NH-C(=O)R⁹ wherein R⁹ represents
C₁₋₆alkyl optionally substituted with cycloC₃₋₁₂alkyl, C₁₋₆alkyloxy,
C₁₋₆alkyloxycarbonyl, aryl, aryloxy, thienyl, pyridinyl, mono- or
di(C₁₋₆alkyl)amino, C₁₋₆alkylthio, benzylthio, pyridinylthio or
pyrimidinylthio;
cycloC₃₋₁₂alkyl; cyclohexenyl; amino; arylcycloC₃₋₁₂alkylamino;
mono-or-di(C₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxycarbonylC₁₋₆alkyl)amino; mono- or
di(C₁₋₆alkyloxycarbonyl)amino; mono-or di(C₂₋₆alkenyl)amino; mono- or
di(arylC₁₋₆alkyl)amino; mono- or diarylamino; arylC₂₋₆alkenyl;
furanylC₂₋₆alkenyl; piperidinyl; piperazinyl; indolyl; furyl; benzofuryl;
tetrahydrofuryl; indenyl; adamantyl; pyridinyl; pyrazinyl; aryl;
arylC₁₋₆alkylthio or a radical of formula (a-1) ;

a sulfonamid $\text{-NH-SO}_2\text{-R}^{10}$ wherein R^{10} represents C_{1-6} alkyl, mono- or poly halo C_{1-6} alkyl, aryl C_{1-6} alkyl, aryl C_{2-6} alkenyl, aryl, quinolinyl, isoxazolyl or di(C_{1-6} alkyl)amino;

- 5 R^3 and R^4 each independently represent hydrogen; halo; hydroxy; cyano; C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkyloxy C_{1-6} alkyl; C_{1-6} alkylcarbonyl; C_{1-6} alkyloxycarbonyl; C_{2-6} alkenyl; hydroxy C_{2-6} alkenyl; C_{2-6} alkynyl; hydroxy C_{2-6} alkynyl; tri(C_{1-6} alkyl)silane C_{2-6} alkynyl; amino; mono- or di(C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkyloxy C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkylthio C_{1-6} alkyl)amino; aryl; morpholinyl C_{1-6} alkyl or piperidinyl C_{1-6} alkyl; or
- 10 R^2 and R^3 may be taken together to form $\text{-R}^2\text{-R}^3\text{-}$, which represents a bivalent radical of formula $\text{-(CH}_2\text{)}_3\text{-}$, $\text{-(CH}_2\text{)}_4\text{-}$, $\text{-(CH}_2\text{)}_5\text{-}$, $\text{-(CH}_2\text{)}_6\text{-}$, -CH=CH-CH=CH- , $\text{-Z}_4\text{-CH=CH-}$, $\text{-CH=CH-Z}_4\text{-}$, $\text{-Z}_4\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-Z}_4\text{-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-CH}_2\text{-Z}_4\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-Z}_4\text{-}$, $\text{-Z}_4\text{-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-Z}_4\text{-CH}_2\text{-}$ or $\text{-CH}_2\text{-CH}_2\text{-Z}_4\text{-}$, with Z_4 being O, S, SO_2 or NR^{11} wherein R^{11} is hydrogen, C_{1-6} alkyl, benzyl or C_{1-6} alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted with C_{1-6} alkyl.

- or R^3 and R^4 may be taken together to form a bivalent radical of formula
- 20 -CH=CH-CH=CH- or $\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$;
- R^5 represents hydrogen; cyclo C_{3-12} alkyl; piperidinyl; oxo-thienyl; tetrahydrothienyl, aryl C_{1-6} alkyl; C_{1-6} alkyloxy C_{1-6} alkyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or C_{1-6} alkyl optionally substituted with a radical $\text{C(=O)NR}_x\text{R}_y$, in which R_x and R_y , each independently are hydrogen, cyclo C_{3-12} alkyl, C_{2-6} alkynyl or C_{1-6} alkyl optionally
- 25 substituted with cyano, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, furanyl, pyrrolidinyl, benzylthio, pyridinyl, pyrrolyl or thienyl;

Y represents O or S;

or Y and R^3 may be taken together to form $\text{=Y-R}^3\text{-}$ which represents a radical of formula

- 30 -CH=N-N= (c-1);
 -N=N-N= (c-2); or
 -N-CH=CH- (c-3);

- aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, phenoxy, nitro, amino, thio, C_{1-6} alkylthio, halo C_{1-6} alkyl, polyhalo C_{1-6} alkyl, polyhalo C_{1-6} alkyloxy, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, cyano, -CO-R^{12} , -CO-OR^{13} ,
- 35

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-NR¹³SO₂R¹², -SO₂-NR¹³R¹⁴, -NR¹³C(O)R¹², -C(O)NR¹³R¹⁴, -SOR¹², -SO₂R¹²;
 wherein each R¹², R¹³ and R¹⁴ independently represent C₁₋₆alkyl; cycloC₃₋₆alkyl;
 phenyl; phenyl substituted with halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy,
 haloC₁₋₆alkyl, polyhaloC₁₋₆alkyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl or
 oxazolyl;

5

and when the R¹-C(=X) moiety is linked to another position than the 7 or 8 position,
 then said 7 and 8 position may be substituted with R¹⁵ and R¹⁶ wherein either one or
 both of R¹⁵ and R¹⁶ represents C₁₋₆alkyl, C₁₋₆alkyloxy or R¹⁵ and R¹⁶ taken together may
 form a bivalent radical of formula -CH=CH-CH=CH-.

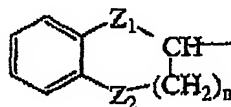
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2. A radiolabelled compound according to claim 1, characterized in that,
 X represents O; C(R⁶)₂ with R⁶ being hydrogen or aryl ; or N-R⁷ with R⁷ being amino
 or hydroxy;

15

R¹ represents C₁₋₆alkyl, aryl; thienyl; quinoliny; cycloC₃₋₁₂alkyl or
 (cycloC₃₋₁₂alkyl)C₁₋₆alkyl, wherein the cycloC₃₋₁₂alkyl moiety optionally may
 contain a double bond and wherein one carbon atom in the cycloC₃₋₁₂alkyl moiety
 may be replaced by an oxygen atom or an NR⁸-moiety with R⁸ being benzyl or
 C₁₋₆alkyloxycarbonyl ; wherein one or more hydrogen atoms in a C₁₋₆alkyl-moiety
 or in a cycloC₃₋₁₂alkyl-moiety optionally may be replaced by C₁₋₆alkyl,
 haloC₁₋₆alkyl, hydroxy, C₁₋₆alkyloxy, arylC₁₋₆alkyloxy, halo, aryl, mono- or
 di(C₁₋₆alkyl)amino, C₁₋₆alkyloxycarbonylamino, halo, piperazinyl, pyridinyl,
 morpholinyl, thienyl or a bivalent radical of formula -O- or -O-CH₂-CH₂-O-;
 or a radical of formula (a-1)

20



a-1

25

wherein Z₁ is a single covalent bond, O or CH₂;

Z₂ is a single covalent bond, O or CH₂;

n is an integer of 0, 1, or 2 ;

30

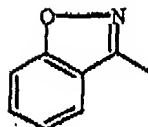
and wherein each hydrogen atom in the phenyl ring independently
 may optionally be replaced by halo or hydroxy;

or X and R¹ may be taken together with the carbon atom to which X and R¹ are
 attached to form a radical of formula (b-1), (b-2) or (b-3);

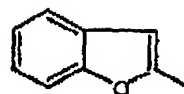
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b-1



b-2



b-3

- R^2 represents hydrogen; halo; cyano; C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkylthio;
 C_{1-6} alkylcarbonyl; C_{1-6} alkyloxycarbonyl; C_{2-6} alkenyl; hydroxy C_{2-6} alkenyl;
 C_{2-6} alkynyl; hydroxy C_{2-6} alkynyl; tri(C_{1-6} alkyl)silane C_{2-6} alkynyl; amino; mono- or
 5 di(C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkyloxy C_{1-6} alkyl)amino; mono- or
 di(C_{1-6} alkylthio C_{1-6} alkyl)amino; aryl; aryl C_{1-6} alkyl; aryl C_{2-6} alkynyl;
 C_{1-6} alkyloxy C_{1-6} alkylamino C_{1-6} alkyl;
 aminocarbonyl optionally substituted with C_{1-6} alkyloxycarbonyl C_{1-6} alkyl;
 10 a heterocycle selected from thienyl, furanyl, thiazolyl and piperidinyl, optionally
 N-substituted with morpholinyl or thiomorpholinyl;
 a radical $-NH-C(=O)R^9$ wherein R^9 represents C_{1-6} alkyl optionally substituted with
 cyclo C_{3-12} alkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, aryl, aryloxy, thienyl,
 pyridinyl, mono- or di(C_{1-6} alkyl)amino, C_{1-6} alkylthio, benzylthio, pyridinylthio or
 15 pyrimidinylthio; cyclo C_{3-12} alkyl; cyclohexenyl; amino; arylcyclo C_{3-12} alkylamino;
 mono- or di(C_{1-6} alkyl)amino; mono- or di(C_{1-6} alkyloxycarbonyl C_{1-6} alkyl)amino;
 mono- or di(C_{1-6} alkyloxycarbonyl)amino; mono- or di(C_{2-6} alkenyl)amino; mono- or
 di(aryl C_{1-6} alkyl)amino; mono- or diarylamino; aryl C_{2-6} alkenyl; furanyl C_{2-6} alkenyl;
 piperidinyl; piperazinyl; indolyl; furyl; benzofuryl; tetrahydrofuryl; indenyl;
 20 adamantyl; pyridinyl; pyrazinyl; aryl or a radical of formula (a-1);
 a sulfonamid $-NH-SO_2-R^{10}$ wherein R^{10} represents C_{1-6} alkyl, mono- or poly
 halo C_{1-6} alkyl, aryl C_{1-6} alkyl or aryl;
 R^3 and R^4 each independently represent hydrogen; C_{1-6} alkyl; C_{1-6} alkyloxy C_{1-6} alkyl;
 C_{1-6} alkyloxycarbonyl; or
 25 R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of
 formula $-(CH_2)_4-$, $-(CH_2)_5-$, $-Z_4-CH=CH-$, $-Z_4-CH_2-CH_2-CH_2-$ or $-Z_4-CH_2-CH_2-$,
 with Z_4 being O, S, SO_2 or NR^{11} wherein R^{11} is hydrogen, C_{1-6} alkyl, benzyl or
 C_{1-6} alkyloxycarbonyl; and wherein each bivalent radical is optionally substituted
 with C_{1-6} alkyl;
 30 or R^3 and R^4 may be taken together to form a bivalent radical of formula
 $-CH=CH-CH=CH-$ or $-CH_2-CH_2-CH_2-CH_2-$;
 R^5 represents hydrogen; piperidinyl; oxo-thienyl; tetrahydrothienyl, aryl C_{1-6} alkyl;
 C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or C_{1-6} alkyl optionally substituted with a radical

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$C(=O)NR_xR_y$, in which R_x and R_y , each independently are hydrogen, cyclo C_{3-12} alkyl, C_{2-6} alkynyl or C_{1-6} alkyl optionally substituted with cyano, C_{1-6} alkyloxy or C_{1-6} alkyloxycarbonyl;

Y represents O or S;

5 or Y and R^5 may be taken together to form $=Y-R^5$ which represents a radical of formula

$-CH=N-N=$ (c-1); or

$-N=N-N=$ (c-2);

10 aryl represents phenyl or naphthyl optionally substituted with one or more substituents selected from halo, C_{1-6} alkyloxy, phenyloxy, mono- or di(C_{1-6} alkyl)amino and cyano;

and when the $R^1-C(=X)$ moiety is linked to another position than the 7 or 8 position, then said 7 and 8 position may be substituted with R^{15} and R^{16} wherein either one or both of R^{15} and R^{16} represents C_{1-6} alkyl or R^{15} and R^{16} taken together may form a

15 bivalent radical of formula $-CH=CH-CH=CH-$.

3. A radiolabelled compound according to any one of claims 1 - 2, characterized in that,

X represents O;

20 R^1 represents C_{1-6} alkyl; cyclo C_{3-12} alkyl or (cyclo C_{3-12} alkyl) C_{1-6} alkyl, wherein one or more hydrogen atoms in a C_{1-6} alkyl-moiety or in a cyclo C_{3-12} alkyl-moiety optionally may be replaced by C_{1-6} alkyloxy, aryl, halo or thienyl;

R^2 represents hydrogen; halo; C_{1-6} alkyl or amino;

R^3 and R^4 each independently represent hydrogen or C_{1-6} alkyl; or

25 R^2 and R^3 may be taken together to form $-R^2-R^3-$, which represents a bivalent radical of formula $-Z_4-CH_2-CH_2-CH_2-$ or $-Z_4-CH_2-CH_2-$ with Z_4 being O or NR^{11} wherein R^{11} is C_{1-6} alkyl; and wherein each bivalent radical is optionally substituted with C_{1-6} alkyl;

or R^3 and R^4 may be taken together to form a bivalent radical of formula

30 $-CH_2-CH_2-CH_2-CH_2-$;

R^5 represents hydrogen;

Y represents O; and

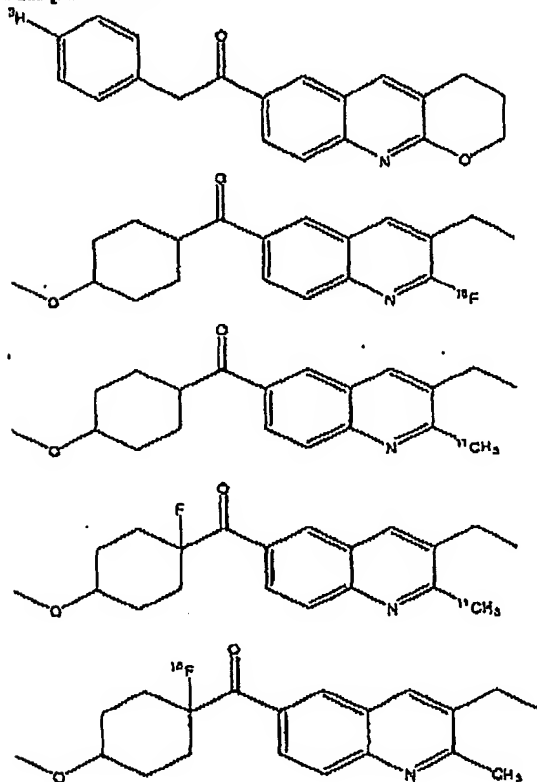
aryl represents phenyl optionally substituted with halo.

35 4. A radiolabelled compound according to any one of claims 1-3, characterized in that the $R^1-C(=X)$ moiety is linked to the quinoline or quinolinone moiety in position 6.

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5. A radiolabelled compound according to any one of claims 1 - 4, characterized in that the compound contains at least one radioactive atom.
6. A radiolabelled compound according to claim 5, characterized in that the radioactive isotope is selected from the group of ^3H , ^{11}C and ^{18}F .

7. A radiolabelled compound according to claim 6, characterized in that the compound is :



8. Radioactive composition for the administration to mammals comprising a therapeutically effective amount of a radiolabelled compound of Formula (I-A)* or (I-B)* and a pharmaceutically acceptable carrier or diluent.
9. A radiolabelled compound or composition according to any one of claims 1-8 for use in a diagnostic method.

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10. A radiolabelled compound or composition according to claim 9, characterized in that the diagnostic method consists of marking or identifying a mGlu1 receptor in biological material.
- 5 11. A radiolabelled compound or composition according to claim 10, characterized in that the marking consists of administering the radiolabelled compound to biological material and the identifying consists of detecting the emissions from the radiolabelled compound.
- 10 12. A radiolabelled compound or composition according to claim 9, characterized in that the diagnostic method consists of screening whether a test compound has the ability to occupy or bind to a mGlu1 receptor in biological material.
13. A radiolabelled compound or composition according to any one of claims 10 - 12,
15 characterized in that the biological material is selected from the group of tissue samples, plasma fluids, body fluids, body parts and organs originating from warm-blooded animals and warm-blooded animals *per se*, in particular humans.
14. Use of a radiolabelled compound or composition according to any one of claims
20 1 - 8 for the manufacture of a diagnostic tool for marking or identifying an mGlu1 receptor in biological material.
15. Use of a radiolabelled compound or composition according to claim 14,
25 characterized in that the marking consists of administering the radiolabelled compound to biological material and the identifying consists of detecting the emissions from the radiolabelled compound.
16. Use of a radiolabelled compound or composition according to any one of claims 1-
30 8 for the manufacture of a diagnostic tool for screening whether a test compound has the ability to occupy or bind to a mGlu1 receptor in biological material
17. Use of a radiolabelled compound or composition according to any of claims 1- 8
35 for the manufacture of a diagnostic tool for imaging an organ, characterized by administering a sufficient amount of a radiolabelled compound or composition according to any one of claims 1-8 in an appropriate composition to biological material, whereby said radiolabelled compound binds to a mGlu1 receptor sites in

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the biological material ; and detecting the emissions from the radiolabelled compound.

- 5 18. Use of a radiolabelled compound or composition according to claim 17 for the manufacture of a diagnostic tool for imaging an organ, characterized in that the imaging is performed using Positron Emission Tomography (PET).
- 10 19. Use of a radiolabelled compound or composition according to any one of claims 14 to 18, characterized in that the biological material is selected from the group of tissue samples, plasma fluids, body fluids, body parts and organs originating from warm-blooded animals and warm-blooded animals *per se*, in particular humans.

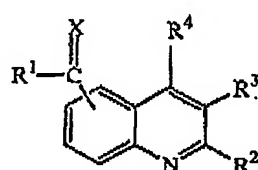
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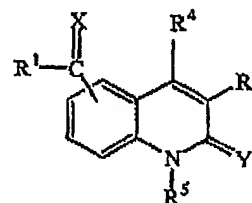
ABSTRACT

RADIOLABELLED QUINOLINE AND QUINOLINONE DERIVATIVES AND 5 THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR LIGANDS.

The present invention is concerned with radiolabelled quinoline and quinolinone derivatives according Formula (I-A)* or (I-B)* showing metabotropic glutamate
10 receptor antagonistic activity, in particular mGlu1 receptor activity, and their preparation ; it further relates to compositions comprising them, as well as their use for marking and identifying metabotropic glutamate receptor sites and for imaging an organ.



(I-A)*



(I-B)*

In a preferable embodiment, X represents O; R¹ represents C₁₋₆alkyl; cycloC₃₋₁₂alkyl or (cycloC₃₋₁₂alkyl)C₁₋₆alkyl, wherein one or more hydrogen atoms in a C₁₋₆alkyl-moiety
or in a cycloC₃₋₁₂alkyl-moiety optionally may be replaced by C₁₋₆alkyloxy, aryl, halo or
thienyl; R² represents hydrogen; halo; C₁₋₆alkyl or amino; R³ and R⁴ each independently
20 represent hydrogen or C₁₋₆alkyl; or R² and R³ may be taken together to form -R²-R³-,
which represents a bivalent radical of formula -Z₄-CH₂-CH₂-CH₂- or -Z₄-CH₂-CH₂-
with Z₄ being O or NR¹¹ wherein R¹¹ is C₁₋₆alkyl; and wherein each bivalent radical is
optionally substituted with C₁₋₆alkyl; or R³ and R⁴ may be taken together to form a
bivalent radical of formula -CH₂-CH₂-CH₂-CH₂-; R⁵ represents hydrogen; Y represents
25 O; and aryl represents phenyl optionally substituted with halo. Most preferred are
radiolabelled compounds in which the radioactive isotope is selected from the group of
of ³H, ¹¹C and ¹⁸F. The invention also relates to their use in a diagnostic method, in
particular for marking and identifying a mGluR1 receptor in biological material, as well
as to their use for imaging an organ, in particular using PET.

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